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THE URINARY EXCRETION OF CALCIUM AND PHOSPHORUS AFTER SURGERY

K. N. WYNNE, M.Sc., S. H. CHORLTON, B.Sc., and
KENNETH W. STARR, F.R.C.S.(Eng.), F.R.A.C.S., F.A.C.S.(Hon.),
Sydney, New South Wales, Australia

THERE IS a marked clinical impression that surgery can accelerate the growth and spread of metastases in patients suffering from certain types of neoplastic disease. It can be deduced that this impression is widely held by the publication of a number of investigations directly inspired by the possibility. As all such studies to date have been restricted to mice or rat experimentation, there will always be some doubt that the conclusions reached will apply to human beings.

This report deals with the first results of a study on the effects of surgery on human patients. Prime attention has been given to calcium metabolism in view of the observations of Coman which suggest that changes in tissue levels of calcium may influence the spread of cancer cells.

As previously reported work on postoperative calcium and phosphorus metabolism has been concerned with long-term daily balance studies, it was decided to restrict this investigation to transient changes in urinary excretion rates for 3 days following operation. A preliminary note on the results of this study has been published (4).

From the Special Unit, New South Wales State Cancer Council, Prince of Wales Hospital, Randwick, New South Wales, Australia.

METHODS

Twenty-three patients (Tables I and II) were studied over a minimum period of 2 days before, and 3 days after, operation. Urine was collected from all patients on a 4 hourly basis with the exception of the first 8 patients studied, on whom some 24 hour and 12 hour collections were made in the preoperative period.

All urine aliquots were acidified with hydrochloric acid and stored at 4 degrees C.

Calcium was determined colorimetrically by using plasmocorinth B and urinary phosphate by a micromodification of the Allen procedure.

The urine of some patients was analyzed for sodium and potassium by flame photometry with the Beckman Model DU spectrophotometer equipped with flame photometer and photomultiplier attachments.

A small tracer dose of calcium 45 was

TABLE I.—EXTENSIVE ABDOMINAL OPERATIONS

Pt. No. *Sex* *Age, yrs.*	*Operation*	*Mean preoperative excretion rates**		
		Urine ml./hour	*Phosphorus mgm.P/hour*	*Calcium mEq./hour*
86 M 49	Abdominoperineal resection	39±24†	19±10†	0.26±0.13†
175 F 48	Polya gastrectomy	102±61†	28±14†	0.15±0.08†
186 F 51	Cholecystectomy	67±40†	22±11†	0.34±0.17†
190 M 28	Polya gastrectomy	20±12†	34±17†	0.20±0.10†
246 F 71	Total hysterectomy	82±56	26±9	0.33±0.14
386 F 56	Choledochotomy	35±20	11±7	0.095±0.065
393 M 59	Resection of sigmoid colon	64±38	24±11	0.16±0.07
453 F 61	Resection of sigmoid colon	63±54	22±10	0.18±0.13
496 M 67	Abdominoperineal resection	27±19	15.5±7.5	0.28±0.16
524 F 42	Excision of hepatic metastases	37±39	10±5	0.075±0.050
592 F 77	Resection of sigmoid colon	91±38	31±10	0.23±0.10
782 F 44	Radical mastectomy and r. salpingo-oophorectomy	48±43	32±15	0.39±0.18
788 M 49	Partial gastrectomy	79±61	29±17	0.54±0.23
804 F 56	Ileotransverse colostomy	63±42	26±9	0.40±0.15

*Plus or minus standard deviation of mean except where otherwise indicated.
†An assumed standard deviation (see text).

administered to 12 patients at the beginning of the collection period. The changes observed in the specific activity of the urinary calcium will be the subject of a separate communication.

RESULTS

All experimental results were initially expressed in the form of a graph relating excretion rate to the time before or after operation (Fig. 1). However, in order to assess objectively the findings of the study, it was found necessary to score the postoperative excretion rates of each 4 hourly period by comparing with the respective mean preoperative excretion rates (Tables I and II). Any postoperative rate outside 1 or 2 standard deviations of the mean preoperative rate was recorded. In the case of patients whose urine was collected 24 hourly before opera-

TABLE II.—EXTENSIVE SUPERFICIAL OPERATIONS

Pt. No. Sex Age, yrs.	*Operation*	*Mean preoperative excretion rates**		
		Urine ml./hour	*Phosphorus mgm.P/hour*	*Calcium mEq./hour*
185 F 30	Radical excision of inguinal lymph nodes	59±36†	33±17†	0.27±0.14†
186 F 51	Radical excision of axillary lymph nodes	45±27†	29±15†	0.34±0.17†
255 F 77	Excision of large organized hematoma popliteal fossa	46±28†	19±10†	0.24±0.12†
351 F 6	Synovectomy for hypertrophic synovitis, both knee joints	27±16†	19±10†	0.19±0.10†
360 M 47	Radical excision of cervical lymph nodes	45±24	31±20	0.17±0.14
517 M 64	Radical excision of axillary lymph nodes	62±37	20±9	0.10±0.04
611 M 39	Radical excision of inguinal lymph nodes and malignant melanoma from thigh	47±15	30±7	0.54±0.20
631 M 29	Radical excision of axillary lymph nodes	64±40	34±26	0.25±0.15
703 F 80	Mastectomy	32±25	11±6	0.13±0.09

*Plus or minus standard deviation of mean except where otherwise indicated.
†An assumed standard deviation (see text).

tion, a standard deviation of 60 per cent of the mean was assumed for urine excretion and 50 per cent of the mean for calcium and phosphorus excretions.

The results of this appraisal suggested a division of patients into two groups according to operation. Table I lists 14 patients (group 1) who underwent extensive operations involving exposure of the body cavity, and Table II, 9 patients (group 2) whose operations were extensive superficial dissections.

Figures 2 and 3 present the results obtained from the patients in groups 1 and 2 respectively.

Oliguria after operation was observed in both groups with a tendency for a longer duration in group 2. It should be noted, however, that owing to the high standard deviations of many of the mean preoperative excretion rates, falls to oliguric levels were often not scored as such. For the same reason, falls of more than 2 standard deviations were, for the majority of patients, not possible.

Urinary diuresis was a feature of both groups with some patients in group 2 excreting large volumes within 24 hours of operation.

There was marked phosphorus diuresis exhibited by patients of group 1. It occurred from 4 to 20 hours after operation with a peak incidence in the 8 to 12 hour period. Group 2 showed some evidence of an increase in phosphorus excretion during the first 24 hours but not to the same extent as group 1.

Both groups featured a lowered excretion of phosphorus during the final 24 hours of the study.

In each group a majority of patients exhibited a fall in urinary calcium excretion after operation. This was more profound and extended longer in the group of ab-

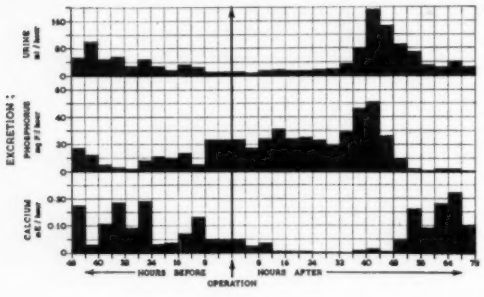

FIG. 1.

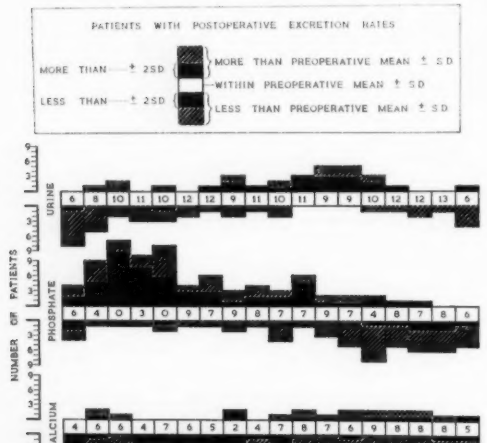

FIG. 2.

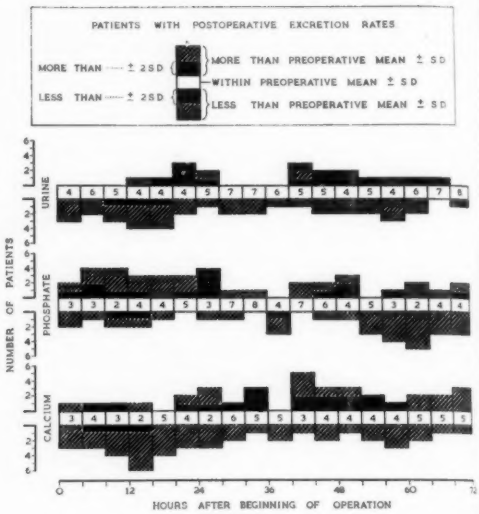

FIG. 3.

FIG. 1. The rates of excretion of urine, urinary phosphorus, and urinary calcium for patient No. 386 undergoing choledochotomy for carcinoma of the common bile duct.

FIG. 2. An incidence graph showing the alterations in urine, urinary phosphate, and urinary calcium excretion rates for 14 patients after extensive abdominal operations (group 1). Each postoperative excretion rate for a 4 hourly period has been scored by comparison with the individual patient's own mean preoperative rate and standard deviation (see text and Table I). Missing data may be perceived when addition of the number of patients in the 5 possible categories do not total 14.

FIG. 3. An incidence graph of the same form as Figure 2 but representing the results obtained with 9 patients undergoing extensive superficial dissections (group 2, Table II).

dominal surgery patients. A subsequent calcium diuresis was a common feature particularly after operations of the group 2 type.

DISCUSSION

Due to the size of our surgical unit, it was not possible to reduce variables by restricting the study to one or two types of operation or by selecting a uniform group of patients. However, to compensate for the disadvantages of such a design, it is considered that the variety of surgical procedures studied have enabled results to be obtained which more truly reflect the general responses to surgery than has been the case with previous studies which were more selective.

The apparent longer period of oliguria of the group 2 patients compared to those of group 1 is probably attributable to the higher proportion of extremely variable preoperative excretion rates in the latter and the practice of not always compensating with intravenous therapy after operations of the former group type.

It has been reported that a phosphorus diuresis usually occurs on the first postoperative day. The present study confirms this observation for operations involving celiotomy. If such operations are assumed to be more traumatic than those of group 2, the

results can be interpreted as indicating that the increase in phosphorus excretion is related to the degree of adrenocortical response provoked by the operation. This is in accordance with the suggestion of Eliel and associates that phosphorus is derived from the intracellular component of skeletal muscle as a consequence to the posttraumatic increase in adrenocortical steroid production.

The decrease in calcium excretion after operation could be due to a cessation of calcium intake. Against this as the sole explanation is the promptness with which calcium retention has been observed to follow operation. Low plasma citrate levels have been reported postoperatively, probably as a result of adrenocortical hyperactivity. This could cause a lowering of the level of plasma complexed calcium, which, in turn, has been shown to influence markedly the rate of calcium excretion.

To explain increases in calcium excretion after operation, Eliel and associates postulated bone resorption as a mechanism for providing small amounts of phosphorus during the period of phosphorus retention. However, where a calcium diuresis has been observed, particularly in group 2, it is frequently associated with an appreciable excretion of phosphorus and generally preceded the appearance of low phosphorus excretion rates. It is therefore suggested that the excretion pattern is more typical of parathyroid stimulation as a result of a calcium deficit than a lack of phosphorus.

Although the results of this investigation may be interpreted and explained in a number of different ways, there still remains a possibility that operative trauma may cause a disturbance in calcium metabolism which could influence tissue calcium concentrations at a local or systemic level. With this in mind investigations are proceeding with the use of the radioisotopes, calcium 45, and calcium 47.

SUMMARY

Urinary excretions of calcium and phosphorus, based on 4 hourly urine collections from 23 patients, are presented for the 3 days following extensive operations.

Fourteen patients who underwent extensive abdominal operations showed; (a) marked phosphorus diuresis with a peak incidence 8 to 12 hours after operation; (b) phosphorus retention beginning 2 days after operation; (c) postoperative retention of urinary calcium.

Nine patients whose operations were classed as extensive superficial dissections exhibited a similar but much less marked pattern of excretion. A calcium diuresis was a frequent feature of this group.

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ENVIRONMENTAL TEMPERATURE OF HUMAN FETUS

GIOVANNI GALLETTI, M.D., Newark, New Jersey

IT HAS BEEN REPORTED that under normal conditions a rather marked difference in temperature exists among the different organs and soft tissues of the body, both in man and in experimental animals. According to the findings reported in the literature, it seems that most investigators question the term "body temperature" as it is used today, and quite properly so, for any one site in the body of an individual can hardly be used as representative of the body temperature as a whole.

The present investigation was undertaken to fill the gap in existing information available in the literature pertinent to the environmental temperature of the human fetus or to the variations in the body temperature of the fetus itself. The aim was to attempt to determine the environmental temperature of the human fetus by the study of a series of recordings of the amniotic fluid, with the intent to establish thereby approximations of the temperature of the human fetus itself through comparison with maternal temperatures.

Perhaps the conclusions reached by Burton and Edholm and the evidence accumulated by others would discourage anyone from attempting to equate the body temperature of the fetus with the temperature of its environment. In the fetus, the skin surface and the body weight ratio is such that the environmental temperature of the fetus should certainly play a great part in the regulation of the body temperature. The very fluid nature of the fetal environment would seem to support this thesis. Furthermore, the human fetus apparently has a thermoregulating system poorly developed throughout intrauterine life and for some time after birth.

From the Department of Surgery of the Buffalo Children's Hospital, and the Department of Surgery of the School of Medicine of the University of Buffalo, Buffalo, New York.

CLINICAL STUDY

Twenty observations were conducted in 20 patients. In each case the rectal temperature, amniotic fluid temperature, and the temperature of the cervix or the uterus were recorded. For this purpose a multi-channel thermistemp tele-thermometer was employed. A standard thermocouple was used for the patient's rectal temperature. For the recording of the amniotic fluid and the temperature of the cervix and the uterus, a 22 gauge thermocouple needle was utilized.

The 20 patients were divided into three separate groups. The first group included those patients who had had a spontaneous onset of labor. In the second group were patients in whom the labor was induced; and in the third group were placed the patients who underwent elective cesarean section. In the first and second groups, the temperatures of the cervix and amniotic fluid were recorded just prior to the breaking of the amniotic membranes. Under vision, the thermocouple needle was first inserted into the cervix, then was digitally inserted through the amniotic membrane. In the third group, the temperatures of the uterus as well as the amniotic fluid were recorded at the moment of laparotomy. First the temperature of the uterus was recorded then, after the exposure of the amniotic sac, the temperature of the amniotic fluid was taken.

Table I shows the results obtained in patients undergoing spontaneous onset of labor. Four observations were made in this group. The temperature of the amniotic fluid in all 4 cases was above 37 degrees C. The temperature of the cervix appeared lower than that of the amniotic fluid, however, with a low temperature differential. The rectal temperature was found to be

TABLE I.—STUDY OF THE AMNIOTIC FLUID TEMPERATURE IN PATIENTS WITH SPONTANEOUS ONSET OF LABOR

		Temperature in degrees C.				
No.	Age, yrs.	Rectal	Cervix	Amn. fl.*	Temp. diff. I†	Temp. diff. II‡
1	30	36.9	37.7	37.9	0.2	1.0
2	21	36.8	37.2	37.4	0.2	0.6
3	31	37.0	37.1	37.7	0.6	0.7
4	24	36.8	37.0	37.8	0.8	1.0

TABLE II.—STUDY OF AMNIOTIC FLUID TEMPERATURE IN PATIENTS WITH INDUCED LABOR

		Temperature in degrees C.				
No.	Age, yrs.	Rectum	Cervix	Amn. fl.	Temp. diff. I	Temp. diff. II
1	30	36.9	36.5	37.5	1.0	0.6
2	35	36.8	36.7	37.5	0.8	0.7
3	29	37.1	36.8	37.4	0.6	0.3
4	19	36.6	36.4	36.7	0.3	0.1
5	33	36.8	37.0	37.8	0.8	1.0

TABLE III.—STUDY OF THE AMNIOTIC FLUID TEMPERATURE IN PATIENTS WITH ELECTIVE CESAREAN SECTION

		Temperature in degrees C.					
No.	Age, yrs.	Rectum	Uterus	Amn. fl.	Temp. diff. I	Temp. diff. II	Anesthesia
1	33	36.9	35.6	35.8	0.2	1.1	Spinal
2	21	37.3	35.5	36.0	0.5	1.3	General
3	21	36.9	36.0	36.2	0.2	0.7	Spinal
4	36	36.7	33.8	34.0	0.2	2.7	General
5	29	36.7	33.6	35.0	1.4	1.7	Spinal
6	28	36.8	33.0	33.4	0.4	3.4	General
7	22	36.9	33.9	34.7	0.8	2.2	Spinal
8	31	36.7	34.4	35.2	0.8	1.5	Spinal
9	36	37.0	35.8	36.2	0.4	0.8	General
10	22	37.1	35.7	36.4	0.7	0.7	General
11	25	36.9	33.4	34.8	1.4	2.1	Spinal

*Amn. fl. Amniotic fluid.
†Temp. diff. I; temperature differential between the amniotic fluid and the cervix.
‡Temp. diff. II; temperature differential between the amniotic fluid and the rectum.

within normal limits in all 4 cases in this particular group.

Table II includes the patients in whom labor was induced. Five patients are included in this group. Here the amniotic fluid temperature, as in group 1, is above 37 degrees C. The temperature differential between the amniotic fluid and the cervix is larger than in group 1, with the temperature of the cervix below 37 degrees C. Again the rectal temperature appeared within normal limits.

In Table III is a summary of the results obtained in 11 patients in whom cesarean section was electively performed. In this group of patients, contrary to the previous two groups, the temperature of the amniotic fluid was recorded as significantly below 37 degrees C., with the temperature ranging, except in 2 cases, between 34 to 36 degrees C., in 1 case being 33.4 degrees and the other 36.4 degrees C. Here too, the temperature of the amniotic fluid appeared higher than that of the uterus, with the difference in temperature considerably greater than in the previous two groups. The rectal temperature was within normal limits, and the temperature differential in relation to the amniotic fluid appeared to be rather high.

In 6 of the patients in group 3 spinal anesthesia was used; in the remaining 5 patients, general anesthesia. It seems, however, from the results obtained, that the type of anesthesia employed did not appreciably influence the temperature of the amniotic fluid, although in this group the amniotic fluid-uterus temperature differential gradient seems to be considerably higher than in the previous two groups.

SUMMARY AND CONCLUSIONS

Twenty patients were studied to determine the amniotic fluid temperature. This determination was made in an attempt to establish, at least indirectly, the temperature of the human fetus through the temperature of its environment. These 20 patients were divided into three separate groups.

In the two groups of patients in whom the onset of labor was spontaneous or induced the amniotic fluid temperature was above 37 degrees C., whereas in the third group of

patients undergoing elective cesarean section, the amniotic fluid temperature was significantly below 37 degrees C.

According to these results, it would seem that the environmental temperature of the human fetus is below 37 degrees C., ranging between 34 and 36 degrees C. prior to the onset of labor and rising as the labor progresses. This would lead to the assumption that, because of the physical nature of the fetal environment, the body surface-body weight ratio, and the absence of a properly developed thermoregulating mechanism, the mean body temperature of the fetus would be approximately that of its environment. Furthermore, if this were true, it could be concluded that the human fetus lives in a state of mild hypothermia. However attractive this conclusion may seem, it needs further investigation in order to support it.

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A THREE YEAR STUDY OF STAPHYLOCOCCAL DISEASE WITH OBSERVATIONS ON CONTROL

H. TAYLOR CASWELL, M.D., F.A.C.S., KENNETH M. SCHRECK, M.D., NORMAN LEARNER, M.D., W. EMORY BURNETT, M.D., F.A.C.S., ELSIE R. CARRINGTON, M.D., DOMINIC A. DeLAURENTIS, M.D., FRED R. ROGERS, M.D., CHARLES R. SHUMAN, M.D., HOWARD H. STEEL, M.D., F.A.C.S., R. ROBERT TYSON, M.D., F.A.C.S., WILLIAM C. WRIGHT, M.D., N. JANE BLOOMBERG, R.N., and FLORENCE E. BROWN, R.N., Philadelphia, Pennsylvania

THE PAST 3 TO 4 YEARS has been a period of great interest in the problem of hospital staphylococcal disease. Large numbers of articles concerning various aspects of the problem have been published, and conferences relative to it have been a part of the majority of medical meetings. A national conference on hospital acquired staphylococcal disease was held in September of 1958 under the joint sponsorship of the Communicable Disease Center of the United States Public Health Service and the National Research Council. In addition, numerous meetings and symposiums on this subject have been sponsored throughout the nation by state and local public health organizations.

As a result of this interest, the medical profession and its allied services have gained appreciable knowledge as to the epidemiology of these infections and methods of control. The majority of hospitals have established permanent committees on infection whose members have included representatives of the medical profession, nursing services, and administration. During this period of time, it has been realized that hospital acquired staphylococcal disease is not a transitory problem but one which the community and the hospital must face for an indefinite period of time.

From the Temple University Medical Center, Philadelphia.

In this article is presented a 3 year experience with 1,237 patients with clinical staphylococcal disease who were observed at the Temple University Medical Center. In this institution which has 900 beds and 60,000 admissions per year, the over-all, uncorrected incidence of staphylococcal disease in hospital patients is approximately 1.5 per cent.

Observations on the significance of the various aspects of this study and on the methods of control will be included. These observations are made on the basis of our present knowledge and experience, and there is little doubt that in the future some of them could be significantly modified or retracted. The survey has been a joint effort of the clinical departments with the Department of Microbiology, the nursing services, and administration.

METHODS AND MATERIALS

Culture methods. Specimens from patients were routinely inoculated onto the surface of two blood agar plates (2 per cent trypticase soy with 8 per cent defibrinated horse blood). Both plates were incubated overnight at 37 degrees C., one plate aerobically and the other anaerobically.

Nasal specimens from the hospital personnel were obtained with sterile, cotton-tipped swabs moistened in sterile saline. The swabs

were inserted about ½ inch into each nostril and immediately inoculated to a blood agar plate. After overnight aerobic incubation at 37 degrees C., all colonies on the plate were identified. No culture media were employed in this study which were selective of staphylococcus or inhibitive of other organisms.

Coagulase test. This test was performed on all isolated staphylococci regardless of pigment or hemolysis production. Human plasma diluted 1:3 with isotonic saline or desiccated coagulase plasma reconstituted with 5 milliliters of saline per ampule was used. Three colonies of staphylococci were picked from the surface of the blood agar plate and inoculated to a tube containing 0.2 cubic centimeter of plasma. The coagulase test was read after overnight incubation at 37 degrees C. This report is concerned only with coagulase positive staphylococci isolated from personnel carriers or from patients with an actual infection.

Bacteriophage typing of staphylococci. All coagulase positive staphylococci were bacteriophage typed according to the method of Blair and Carr.

NASAL CARRIERS

In a previous paper (1), we have noted a 40 per cent incidence of nasal carriers of coagulase positive staphylococci in 640 hospital personnel who were surveyed. Of those who were healthy nasal carriers, 4 per cent carried the 80/81 bacteriophage strain which was responsible for approximately 70 per cent of all hospital related infections. In September of 1959, a nasal survey was repeated on 100 personnel of the operating room. Once more, there was approximately a 40 per cent incidence of coagulase positive staphylococci in the nares of these individuals. Bacteriophage typing of these organisms did not reveal that any carried the 80/81 strain. The healthy nasal carrier has been reported to play a significant role in cross-infection, particularly in epidemic situations as they involve the nursery and the operating room. Their actual role in transmission of the organism in nonepidemic situations is a most difficult one to evaluate, particularly in view of the fact that the 80/81 strain which is responsible for 70 per cent of hospital related infections has been found on numerous surveys to be an infrequent (0 to 4 per cent) organism in the nares of healthy carriers.

The "sick" or infected carrier can unquestionably play a major role in cross-infection. The role of the so-called healthy carrier in the transmission of staphylococcal disease in our opinion is poorly understood. We believe that there is not sufficient evidence to warrant the establishment of rigid policies in reference to the management of these healthy carriers. It is certainly not practical or warranted to discharge or furlough all personnel carrying staphylococci in the nasal vestibule. "Treatment" of the asymptomatic carrier with antibiotic creams is effective while the agent is being used locally but there is a high rate of reinfestation. This type of treatment also approaches to some degree the indiscriminate use of antibiotics and could play a role in the development of strains resistant to antibiotics to which they are now sensitive. In epidemic situations, local treatment of healthy carriers with the dominant strain may have a place although it is of even greater importance in such a situation to remove these individuals from critical areas such as the nursery, delivery room, and operating rooms.

VIRULENCE

Attempts to carry out virulence studies on laboratory animals have, as a rule, been unproductive. The virulence of the 80/81 strain varies considerably in the individual patient. On the basis of its dominance as the cause of hospital related infections, one must accept the fact that the 80/81 strain has greater facility for transmissibility which could be interpreted as a modality of virulence. In our clinical experience, staphylococcal infections have been associated with the greatest morbidity and mortality in older individuals who have had orthopedic procedures in which internal prostheses

have been used and in diabetics with extensive infections of the extremities requiring amputation. Postoperative staphylococcal infections following chest surgery with the resultant empyema likewise have been major infections.

The majority of staphylococcal surgical infections have been of mild to moderate severity and usually respond well to adequate surgical drainage. In most instances, the use of antibiotic agents has not been required although they are not withheld if there is a significant febrile response or evidence of surrounding cellulitis, lymphangitis, and lymphadenitis.

TABLE I.—STAPHYLOCOCCAL SURGICAL INFECTIONS

	1956	*1957*	*1958*	*Per cent phage type 80/81*
Clean surgical wounds	136	59	55	53
Contaminated surgical wounds	28	50	49	41
Pneumonia in surgical patients	4	4	5	77

STAPHYLOCOCCAL SURGICAL INFECTIONS

Clean surgical wounds. At Temple University Medical Center, there are approximately 10,000 operative procedures performed each year in which staphylococcal infection could conceivably occur. Clean surgical wounds include any operative procedure in which there is not gross contamination at the time of surgery such as drainage of abscesses, oropharyngeal surgery, or similar procedures. Surgical procedures in which the gastrointestinal tract is entered are placed in the category of clean surgical wounds despite the fact that there is invariably some degree of wound contamination as a result of the surgical procedure. We do not believe that a staphylococcal wound infection can be considered to be the result of the invasion of the gastrointestinal tract as the organism is rarely found as a member of the normal flora of the gastrointestinal tract.

During the 3 year study which would include approximately 30,000 operative procedures, 2 group A streptococcal infections have been noted in clean surgical wounds. This is certainly a striking example of the fact that the previously dreaded Streptococcus pyogenes has largely disappeared from the hospital environment. We have also noted that infections of clean surgical wounds with gram-negative organisms have been extremely rare. The gram-negative organisms have been the source of wound infection primarily in those instances in which the wound was exposed to significant contamination from the large bowel or urinary tract, or because of the drainage of intraperitoneal abscesses.

In Table I, it can be observed that staphylococcal sepsis in clean surgical wounds in our institution has remained stationary in 1958 and 1957. In both of the latter years, there were approximately 60 per cent fewer infections in clean surgical wounds than were observed in our original study in 1956. The incidence of staphylococcal wound sepsis in clean surgical wounds computed on the basis of 10,000 operative cases per year has been .55 to .59 per cent during the years 1957 and 1958. The percentage of these infections due to bacteriophage type 80/81 has remained at approximately the same level throughout the 3 year period (53 per cent).

The survey on clean surgical wound infections did not reveal what could be considered any significant difference in the wound infection rate in private patients operated upon by various individual staff surgeons. There were, however, twice as many staphylococcal wound infections in ward patients operated upon by senior residents as compared with statistics on the private patients. The significance of this observation is clouded by multiple variables in these two groups of patients. These include differences in economic status, duration of stay in the ward preoperatively, hospital accommodations, race, time required for the surgical procedure, and the type of surgical disease. The existence of this difference in infection rates, however, points to the need in resident

TABLE II.—STAPHYLOCOCCAL INFECTIONS IN MEDICAL PATIENTS

	1956	*1957*	*1958*	*Per cent phage type 80/81*
Hospital related medical infections...	58	53	68	71
Hospital related pneumonia.....	1	3	2	83
Hospital unrelated pneumonia.....	0	6	13	37

training for emphasis on the fundamentals of surgical technique and wound physiology which too often can be forgotten in the resident's desire to perform as many complicated operations as possible during the senior year of his training.

Contaminated surgical wounds. These wounds include chronic ulcerations, extensive traumatic wounds, and wounds in which there has been long continued drainage, in which it was believed that the staphylococcal sepsis was in some way related to hospitalization. As shown in Table I, there has been a numerical increase in this group from 28 in 1956 to 50 and 49 respectively in 1957 and 1958. It is possible that this increase is due to greater efficacy in reporting these cases. In 41 per cent of them, the staphylococcus was of the 80/81 strain. In many, there was a polybacterial flora. It is doubtful that this type of wound sepsis can ever be completely eliminated because of the nature of the wound itself. This does not mean, however, that every effort to maintain surgical asepsis of these wounds under present facilities should not be maintained. Because a wound is obviously contaminated in no way excuses its treatment with anything other than the same strict sterile technique and attention which would be given to a clean surgical wound.

STAPHYLOCOCCAL INFECTIONS IN MEDICAL PATIENTS

A great majority of these infections were cutaneous lesions ranging from pustules to carbuncles. Many of these individuals had had prolonged periods of observation and hospitalization and frequently were bedfast. It is of interest to note that although the clean surgical wound infection rate decreased appreciably from 1956 to 1958, the incidence of these medical infections rose from 58 cases in 1956 to 68 cases in 1958 (Table II). Seventy-one per cent of these medical infections were produced by phage type 80/81 staphylococcus, the so-called hospital strain. This compares with a 53 per cent incidence of the 80/81 strain in the clean surgical wound infections. These figures reaffirm the concept that staphylococcal disease in the hospital is not the concern of any one department but of all. Control measures are equally important on all services. If this concept is not accepted in an institution, then a reservoir of patients with staphylococcal sepsis is created which continues to contaminate the hospital environment and negate the efforts to control infection within the institution.

STAPHYLOCOCCAL PNEUMONIA

During the 3 years of our study, 38 patients with staphylococcal pneumonia have been observed. Nineteen of these patients were admitted with the disease and had had no previous institutional contact. The criteria for diagnosis were positive x-ray findings of parenchymal involvement and sputum cultures which were predominantly coagulase positive staphylococci. None of the cases of staphylococcal pneumonia was of the lobar variety, and all showed patchy areas of consolidation, typical of bronchopneumonia. The over-all mortality rate of this group was 39 per cent which is approximately the same mortality rate observed in the preantibiotic era.

The incidence of staphylococcal pneumonia in hospitalized patients was extremely low (.001 per cent), and, despite the lack of comparative figures, it would appear that there has been no increase in the incidence of this highly lethal staphylococcal disease in the antibiotic era in this institution.

Staphylococcal pneumonia in nonsurgical patients. As illustrated in Table II, there has been a total of 6 cases of staphylococcal pneumonia in the 3 year period in hospital-

ized medical patients. The 80/81 strain was responsible for 5 (83 per cent) of these 6 staphylococcal infections.

It is interesting to note that there were 19 patients admitted with staphylococcal pneumonia who had had no previous institutional contacts. As illustrated in Table II, 13 of these 19 patients were admitted in 1958, 6 in 1957, and none in 1956. In this group, 7 or 37 per cent were caused by the 80/81 strain. Whether this increase in the number of patients admitted from the community with staphylococcal pneumonia is of significance must be determined by the experience of subsequent years.

Two of the patients in this group were under 35 years old and had a fulminating course, complicating an influenza-like illness. Five patients were over 65, and 6 had severe underlying disease, such as cerebral thrombosis, congestive heart failure, or severe malnutrition and avitaminosis.

Staphylococcal pneumonia in surgical patients. During the 3 year period, there were 13 cases of staphylococcal pneumonia occurring postoperatively in surgical patients (Table I). This represents an incidence of .02 per cent. The 80/81 strain was the responsible organism in 10 of these 13 patients (77 per cent). Nine of these patients had been given an anesthetic by an endotracheal tube, and 4 had received a local or spinal anesthetic. Nine of them had been hospitalized 1 to 3 weeks prior to surgery.

It would appear that, in this small group of patients, prolonged preoperative hospital stay and the use of endotracheal anesthesia played a role in the development of postoperative staphylococcal pneumonia. Of the 4 patients who were operated on promptly after admission, in 2 staphylococcal wound infections had developed prior to the development of the pneumonia.

Antibiotic treatment of staphylococcal pneumonia. Chloramphenicol alone or in combination with novobiocin seemed to be the most effective therapeutic agent. However, despite intensive therapy, the mortality rate for the whole series was 39 per cent. More recently, we have been impressed with the value of kanamycin in this disease.

TABLE III.—STAPHYLOCOCCAL INFECTION IN HOSPITAL PERSONNEL

	1956	*1957*	*1958*
Student nurses	64	41	46
Graduate nurses	15	5	4
Staff	15	9	13
Others	5	2	2
Total	99	57	65

TABLE IV.—HOSPITAL UNRELATED STAPHYLOCOCCAL DISEASE

	1956	*1957*	*1958*
Cases	87	144	184
Per cent phage type 80/81	16	28	27

STAPHYLOCOCCAL INFECTIONS IN HOSPITAL PERSONNEL

Staphylococcal disease in hospital personnel is of major significance in the over-all problem of cross-infection. There is no doubt that patients can become infected by such contacts and in turn transmit staphylococcal disease to other patients and personnel. As illustrated in Table III, the majority of these infections occurred in student nurses who have the most intimate patient contact. We have previously reported (1) that two-thirds of these infections have occurred on body areas exposed to contact contamination in nursing uniform, i.e., hands, wrists, forearms, head, and neck. It is also true that among hospital personnel the student nurse is the individual who has most recently entered the hospital environment and, therefore, theoretically could have the least individual resistance to the organism. The staphylococcal cutaneous infection rate in student nurses in 1956 was 24 per cent and in 1958, 17 per cent. Among graduate nurses, in 1956 there was a staphylococcal cutaneous infection rate of 8 per cent and in 1958 of 2 per cent. Among residents and interns, in 1956 there was a staphylococcal infection rate of 6 per cent and in 1958 of 5 per cent. The infection rate in nonprofessional hospital workers and staff physicians was essentially negligible. These infection rates mirror once more the presence of the organism in the hospital environment and the essential

need for constant education of personnel in the importance of sound sterile technique both during and after patient contact. These infections in personnel almost without exception consisted of furuncles. None of the personnel was seriously ill. All personnel with infection were treated in a central clinic which is a most important factor in the over-all management of the problem, and all were relieved of duty without financial penalty until the infection had cleared. Antibiotics were rarely used.

It is also of interest that in 1956, 80 per cent of the staphylococcal infections in personnel were caused by the 80/81 strain of staphylococcus. In 1958, 69 per cent of the infections were a result of this strain.

The incidence of boils among interns, residents, and nurses has been a problem of some degree in institutions for many years. Certainly, it did not begin with the so-called antibiotic era. It is doubtful that such infections can ever be completely eliminated but the incidence can be appreciably lessened by proper technique and management.

HOSPITAL UNRELATED STAPHYLOCOCCAL DISEASE

These cases represent patients admitted for the treatment of staphylococcal disease without previous hospital contact of any type. As illustrated in Table IV, 87 of these patients were admitted in 1956, 144 in 1957, and 184 in 1958. In 1956, there was a 16 per cent incidence of the 80/81 strain in these patients while, in 1957 and 1958, the incidence of infection with the 80/81 strain rose to 28 per cent.

One cannot avoid being impressed by the fact that over twice as many patients were admitted from the community with staphylococcal disease in 1958 as in 1956. It is a reasonable assumption that the community incidence of staphylococcal disease has appreciably increased during this 3 year period. It is likewise possible that the so-called hospital strain (80/81) is now present in the community to a greater degree.

These cases present a particular problem when one is attempting to eliminate the organism from the hospital environment. With a large community reservoir of staphylococcal disease (184 cases admitted in 1958), there is a constant flow of heavily contaminated patients into the hospital. It is impossible to protect the institutional environment under these circumstances without a separate facility for all patients with infection. This problem will be discussed briefly under observations on control.

ANTIBIOTIC RESISTANCE

In a previous article (1), we presented the antibiotic resistance pattern of the organisms present in hospital acquired staphylococcal disease, using the tube dilution technique. The 80/81 strain at that time showed a 90 to 100 per cent resistance to penicillin, tetracycline, streptomycin, and erythromycin. This strain was highly susceptible to chloramphenicol, novobiocin, bacitracin, and neomycin.

The antibiotic resistance pattern of these 80/81 organisms 2 years later is to be the subject of a separate article. The 80/81 strain continues to show almost complete resistance to penicillin, tetracycline, streptomycin, and erythromycin and, in addition, there is a definite trend of increased resistance to chloramphenicol and novobiocin. Bacitracin and neomycin retain their effectiveness and kanamycin and spontin show a minimal incidence of resistance.

These results point once more to the fact that with increased usage of antibiotic agents there is a concomitant increase in strains resistant to them. Antibiotics which are limited in usage by virtue of toxicity (bacitracin, neomycin) or by the necessity for parenteral administration (kanamycin, spontin) maintain their efficacy.

The use of antibiotic agents in surgical patients has unquestionably been of inestimable value in lowering surgical morbidity and mortality. Unfortunately, they have been administered in many patients in whom there has been little, if any, indication for their usage. This has been particularly

true when they are used prophylactically in "clean" surgical cases and in infections of various types of mild to moderate degree. In the great majority of surgical infections, antibiotics are of an adjunctive nature and play a secondary role to basic surgical treatment. Attempts to use antibiotics in the treatment of infections such as peritonitis without correction or control of the cause of the infection, or in soft tissue infections without adequate drainage are certain to result in failure. Selection of the antibiotic to be used, its dosage, and the duration of therapy must be based on a combination of adequate bacteriologic culture and sensitivity studies and clinical experience. In patients with severe infections requiring antibiotic therapy before cultures can be reported, a thorough knowledge of the antibiotics available and of the organisms most likely causing the infection is invaluable.

Limitation of the use of certain antibiotics within an institution has been effective in certain instances but, of course, is of no value in the control of usage in the medical community at large. It is our belief that further education in antibiotic usage at both the undergraduate and graduate level is needed. "Newer antibiotics" are needed far less than a better understanding of the agents now being used.

OBSERVATIONS ON CONTROL

The over-all problem of the prevention of infection of hospital patients with staphylococci is one which involves every aspect of hospital care. The environmental aspects of this problem have been well documented by Walter and others, particularly in regard to the effects of hospital housekeeping techniques and air-conditioner maintenance. Of equal importance is the technique of hospital personnel and the management of patients with infection. The actual surgical technique used and the wound environment created as a result of it are of real significance in reference to the problem of staphylococcal infections in surgical wounds. As previously stated, a functioning, competent committee on infection is of inestimable value in correlating the multiple moves which must be made in order to accomplish an efficient control program. One of the committee's most important duties is that of education and its ability to instill in hospital personnel a sense of personal responsibility in the prevention of infection in the patients under their care. No institution can make the statement, "we have no infections," without evidence that infection is constantly being searched for in both in-patients and out-patients.

During the past 3 years, a large number of various antiseptic agents have been developed which have been recommended for use in paints, sprays, linens, waxes, laundry rinse water, and the like. There is hardly a hospital department which has not been urged to use one of these agents as a part of its technique. Unfortunately, the great majority of these agents have not been subjected to adequate control studies on a clinical level. There is little doubt that they will kill organisms in the laboratory but whether they will be of any value in actual clinical practice is unknown. All of them add to hospital costs and, generally speaking, their use is unwarranted until better evidence of value is forthcoming.

OPERATING ROOM TECHNIQUE

There should be regular bacteriologic surveys of the efficacy of the various sterilization procedures used in the operating room. Our own studies have not shown any defect in sterilization procedures over the past 3 years. This does not mean that a defect in sterilizing equipment cannot occur. This regular bacteriologic control also emphasizes to the personnel responsible for operating room supplies and for sterilization the importance of their duties.

Scrubbing technique. The preparation of the hands and forearms of operating room personnel for the surgical procedure is as important as the sterilization of the instruments used. Preoperative scrubbing was initiated for a two-fold purpose. One is

adequate mechanical cleansing of the skin with the removal of dirt, debris, and sebum, and the second is the application of an effective germicidal agent to the clean skin after the mechanical cleansing. Whether these two purposes are accomplished by a soap containing a germicide or by plain soap followed by a germicide is not of great importance. It is important, however, to insist on an adequate period of scrubbing and we consider this to be 10 minutes. This is particularly true in an institution where students, student nurses, residents, and interns in addition to graduate personnel are working in the operating room. The importance of personal hygiene should also be emphasized to all personnel, and everyone working in an operating room should have a shower at the beginning of the operating day. Adequate mechanical cleansing of the patient's skin by scrubbing prior to the application of a germicidal agent is an integral part of the scrubbing technique. A thorough cleansing shower should be taken by all patients on the evening prior to operation when this is possible.

Personnel and patients with infection. As previously stated, no one with clinical infection should be allowed to work in the operating room. This should also apply to personnel with respiratory infections. Patients with clinical staphylococcal infection under no circumstances should have elective surgery of any type. It has been our experience and that of others that there is a high incidence of staphylococcal wound infection in these individuals even though the incision may be well removed anatomically from the area of infection. At the present time, it is our feeling that any such elective surgical procedure should be delayed for 2 to 3 months after the complete healing of the staphylococcal lesion.

Anesthesia department. Anesthesia equipment should be subjected to the same rigid bacteriologic control studies as other operating room equipment. The technique of the anesthetist must be of the same high level as that of other operating room personnel, and the same attitude toward members of the department with clinical infection must be enforced. Tubing and masks must be thoroughly cleansed with detergent germicidal solutions between uses.

Surgical technique and wound technique. There is little doubt that careless or ill-advised surgical and wound technique can create an environment in which infection is much more likely to develop. The rough handling of tissues, large bites with hemostats, and unnecessary tying of multiple small vessels which will spontaneously clot—all create circumstances enhancing the possibility of infection. The use of catgut which is a strong tissue irritant should be minimized and, when necessary, the finest grade possible should be used. The use of interrupted wire technique throughout in the closure of the parietes is of value. Saline lavage of both the depths and the superficial layers of the wound should be carried out to remove blood clots and tissue debris. The handling of sharp instruments and needles with the fingers can result in multiple glove perforations which, in turn, can unquestionably contaminate the wound. Many glove perforations can be prevented by proper technique. Needles should always be handled with tissue forceps, and nurses and assistants can be trained to handle sharp retractors and towel clips without exposing the glove to the danger of tearing.

In contaminated cases such as bowel surgery, the "towel technique" should be used. By this technique, the wound is protected with additional drapes from contamination occurring as the result of the opening of the bowel, and all instruments used in the anastomosis are segregated from those which are to be used in the closure of the wound. In addition, after the contaminated portion of the procedure, the surgeon and his assistants change gown and gloves. The suture nurse has not become contaminated during the procedure and, as a result, the parietal wound is protected from the contamination which is certain to occur if this technique is not used.

Local use of antibiotics in surgical wounds. The local use of certain antibiotics is of real value in certain surgical procedures. This is particularly true in surgical operations in which there has been of necessity some bacteriologic contamination of the peritoneum, pleura, and soft tissue wounds as a result of the surgical procedure. Pulaski has called this method of using antibiotics locally "discriminate antibiotic prophylaxis." This applies particularly to large and small bowel surgery and to pulmonary resections of various types. At the time of closure, the local instillation of antibiotics should be carried out in the pleura or in the peritoneum and, in addition, the soft tissue wound should be flooded with this solution. If contamination has occurred at this time, the organisms are still lying superficially in the wound and, with the antibiotic concentrations that are used, are highly susceptible to them. Penicillin (1,000,000 units) and streptomycin (1 gram) in 60 cubic centimeters of solution are commonly used in the peritoneal and pleural cavities. One must, of course, be certain that there is no history of penicillin sensitivity. The decision as to the use of antibiotics locally in the contaminated surgical wound must be individualized. The proper application of this technique can definitely result in decreased morbidity and, on occasion, mortality.

Masks and drapes. Surgical masks in common use are notoriously ineffective, and the longer they are worn the less protection is afforded to the environmental air over the operating table from the exhalations of the surgical personnel. Efforts to improve this situation have been made by other investigators. In most instances, the industrial type masks are uncomfortable, and their cost has been prohibitive. Surgical procedures are difficult enough without adding to them an uncomfortable mask which is a source of constant annoyance. Various groups are working on this problem at the present time and it is hoped that an acceptable, improved surgical mask will be available in the not too distant future.

Protection of the surgical wound from the surrounding skin has depended on the use of towels of various types for many years. As the procedure goes on, these towels become moist and, of course, readily pass bacteria from the patient's skin to their surface. The significance of the role which the patient's skin organisms play in the development of wound infection is unknown except in those individuals who have already established cutaneous infection at the time of the surgical procedure. The use of a plastic drape, adhered to the skin by an adhesive substance, or of a plastic solution sprayed directly on the surrounding skin has been recommended. Both of these measures could be effective agents in protecting the incision from the flora of the patient's skin. It is important to realize that if the plastic drape is used, then the wound should be closed with the drape undisturbed since peeling it back for skin closure negates what benefit might have accrued in protecting it from the skin about the wound during the operative procedure. Inclusion of these agents in surgical technique theoretically would appear to be desirable. However, at present, there is to our knowledge no adequate control study which would point to their efficacy. In institutions where their additional cost would not be a significant factor, their use is warranted. In larger institutions, we doubt the wisdom of using this type of technique without better evidence as to its value.

ISOLATION OF INFECTED PATIENTS

As previously stated, there is a constant seeding of the hospital environment with patients admitted with staphylococcal disease. In addition, the environment is also contaminated by those individuals in whom staphylococcal infection develops during their period of hospitalization. There is little doubt that if true physical isolation of all individuals with infection within an institution could be carried out, the over-all incidence of hospital related infection would fall. This isolation at present in most in-

stitutions consists of barrier nursing in patients with staphylococcal pneumonia and those with severe wound or cutaneous infections. Patients with less severe degrees of infection are not isolated. Although this particular technique is better than no attempt at isolation at all, it obviously is a most deficient one. It would be similar to an isolation technique in severe cases of scarlet fever with the exclusion from isolation of those patients who have what appear to be only moderate cases of the disease. Effective isolation demands physical facilities which are entirely separate from the remainder of the institution and this separation, of course, should also include personnel. It would also demand that, within the isolation unit, patients with minor infections such as furuncles would not be in intimate contact with those with staphylococcal pneumonia and other severe staphylococcal infections. At the present time, in the great majority of institutions, this program is impossible not only on the basis of physical facilities but because of increased costs. However, it is an aspect of the problem of staphylococcal disease which must be considered and it would be of real value in solidifying the attitude toward isolation if studies could be initiated in several large institutions on the results of such a program. The hospital architect of the future must consider such a unit as some part of his planning.

DRESSING CARRIAGE TECHNIQUE

In a previous report (1), we stated our endorsement of having a dressing carriage at all times in the charge of an experienced graduate nurse. This program has been continued throughout the 3 year period, and we still believe that it is an important part of improvement in surgical technique. The nurses in charge of these carriages are included as members of the infection committee and are invaluable because of their constant contact with surgical wounds throughout the institution. Their presence in charge of the carriage ensures the fact that cultures will be taken by less experienced personnel such as interns and residents whenever necessary. The contamination of the environment with dirty dressings is avoided. Contaminated dressings should be placed in paper bags and burned immediately. Contaminated instruments are likewise placed in paper bags and are autoclaved before washing. By using this technique, there have been no staphylococcal infections in our central supply room personnel in over 3 years despite the fact that these individuals clean and package all instruments used throughout the institution. These nurses are also of great value in instructing interns and residents in proper aseptic technique in dressing wounds of various types.

SUMMARY

A 3 year experience with staphylococcal disease observed in a large general hospital has been presented. It is our belief that basic research on the mode of transmission of the organism and its virulence is needed.

The successful prevention of infection in hospital patients depends upon a multiplicity of factors. The foundation of successful prevention depends on well informed personnel who are impressed with the importance of their personal technique in the program. The question of whether or not hospital related staphylococcal infection has increased in the past 10 years is no longer a significant one. The important question as of now is what is being done to learn of its mechanism and epidemiology and of the techniques which will prevent it.

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ELECTROCARDIOGRAPHIC AND HUMORAL CHANGES IN TRANSIENT OCCLUSION OF THE PORTAL VEIN IN THE DOG

CARLOS TANTURI, M.D., F.A.C.S., R. H. MEJÍA, M.D., J. F. CANEPA, Ph.D., and O. T. GOMEZ, M.D., Buenos Aires, Argentina

IT HAS BEEN SHOWN previously (3) that permanent occlusion of the portal vein at its entrance to the liver in the dog is followed by death within an average period of 2 hours and 5 minutes. Thirty minutes after the ligature has been placed, the effective circulating blood volume is reduced to 40 per cent of the initial value. At the end of 90 minutes a further reduction has been found —57 per cent of the initial value (2). The reduced blood volume is due to stagnation of blood in the splenogastrointestinal area, a tributary of the portal vein. This sudden and progressive hypovolemia explains why the concept of shock has been applied to the picture presented by animals succumbing to sudden portal occlusion.

It has been also demonstrated that between 10 and 40 minutes after ligature the electrocardiogram showed depression of ST segments and inverted T waves in 100 per cent of the cases. Between 35 and 60 minutes in aVL leads, an increased prominence of both point J[1] and ST segment together with T wave inversions are registered in the electrocardiogram in the tracings of 63.62 per cent of the animals. In all cases, the changes registered in the electrocardiogram are similar to the basic pattern of subendocardic ischemia due to acute coronary insufficiency. In many instances, a change in the pattern develops, representing a stage beyond ischemia, so a diagnosis of epicardial injury of the high lateral region of the left ventricle has been made in 63.62 per cent of the cases.

In view of the fact that in the majority of animals with acute total occlusion of the portal vein the electrocardiographic changes appeared early, the possibility of producing the epicardial injury by means of a transient occlusion of the portal vein was considered.

METHOD

Twelve dogs of from 8 to 24 kilograms in weight were operated upon under aseptic surgical technique. Nembutal administered intravenously in a dose of 32 milligrams per kilogram was used as anesthesia. After a laparotomy, the portal vein was isolated and a ligature placed around the vein just above its junction with the pancreatic vein. Occlusion of the portal vein was maintained for 45 minutes, then released, and the abdomen closed. The dogs were sent to their cages and antibiotics were given during the postoperative period, 400,000 units of penicillin every 24 hours.

Electrocardiograms were taken at frequent intervals before the ligation, after 15, 30, and 45 minutes, and soon after the vein was released. The conventional leads of Einthoven, the unipolar limb-leads of Goldberger, and the precordial leads of Wilson were employed. The electrocardiographic studies were followed subsequently every 24 hours, until the fifth postoperative day. Arterial blood pressure was recorded through the femoral artery by direct manometric readings before, during, and after the occlusive period of the portal vein.

In these animals, the glutamic-oxalacetic

From the Laboratory of Experimental Pathology and Surgery of the Medical School of the University of Buenos Aires, Buenos Aires, Argentina.

[1]Point J is the union between the S and T waves. When J is elevated, it suggests myocardial injury.

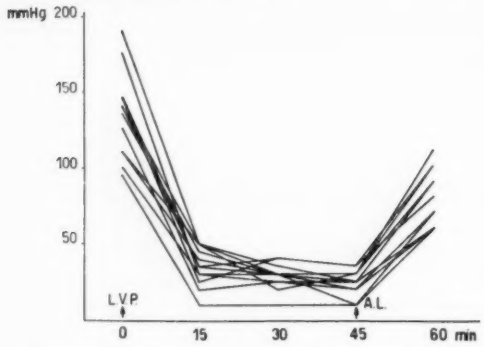

FIG. 1. Variations of systolic blood pressure in 12 dogs subjected to a 45 minute period of occlusion of the portal vein. L. V. P., ligation of portal vein; A. L., ligature released.

transaminase (G.O.T.) activity of plasma was also studied by following the technique of Sall and associates. Blood samples were collected before operation and every 24 hours until the fifth postoperative day.

RESULTS

The transient occlusion of the portal vein for a period of 45 minutes is not followed by death. Variations in the systolic blood pressure are similar to those found in the permanent ligation of the vein. Fifteen minutes after the occlusion has been released, the systolic blood pressure attains almost its original levels (Fig. 1).

TABLE I.—VARIATIONS OF PLASMA CONCENTRATION OF G.O.T. (UNITS PER MILLILITER)

Dog No.	*Before*	*24 hrs.*	*48 hrs.*	*72 hrs.*	*96 hrs.*
			GROUP A		
40	53	123	124	8.1	8.1
41	47.5	280	217	71.7	30.2
44	74	145	107	—	140
45	73	301	205	—	172
49	70	198.5	104	53	54.5
			GROUP B		
43	33.2	115	135.5	14.2	69.5
50	36.7	51	173	109	99
51	89	113	203	94	101.5
			GROUP C		
42	46	48.7	91.5	16.2	46.3
46	81	98	10	11.7	—
47	72.5	168	77	35.7	—
48	89	102	98	49	—

Group a. Animals with infarct which developed during the occlusive period.
Group b. Animals in which a late myocardial infarct developed.
Group c. Animals in which myocardial infarct did not develop.

The electrocardiographic changes were also similar to those found in the permanent occlusion of the portal vein. All cases showed the basic pattern of subendocardial ischemia, and, in 5 cases out of 12, a pattern of epicardial injury of the high lateral region of the left ventricle was registered. In some cases the subendocardial ischemia almost disappeared once the ligature was drawn, but the electrocardiographic changes related to the epicardial injury still remained on the following days with slight variations of intensity (Figs. 2 and 3).

Seven animals which have not shown signs of epicardial injury followed two different patterns. Four out of 7 showed normal electrocardiographic tracings in the course of the following days. The remaining 3 dogs showed an accentuation of their subendocardial lesion which was most prominent in the second postoperative day, and, in 2 of them, signs of late epicardial lesion were registered at this time. These changes were still present when the animals were sacrificed at the end of the fifth postoperative day.

The G.O.T. activity of the plasma paralleled the electrocardiographic changes. In the 5 animals in which the signs of epicardial injury appeared during the period of portal occlusion, a considerable increase of G.O.T. in the plasma was found early at 24 hours after operation, followed by a slow decline in the subsequent days. In the group of 4 dogs which have not shown signs of myocardial infarct during the course of the experiment, no increase above normal values of G.O.T. was observed at any time. In the 3 animals with accentuated subendocardial ischemic lesion which was registered late (48 hours after the vein was released) an increase of the G.O.T. activity of the plasma was found in 2 of them coincident with the electrocardiographic pattern of epicardial ischemic lesion (Fig. 4 and Table I).

COMMENT

It is known that the G.O.T. activity of the plasma increases in patients with myocardial

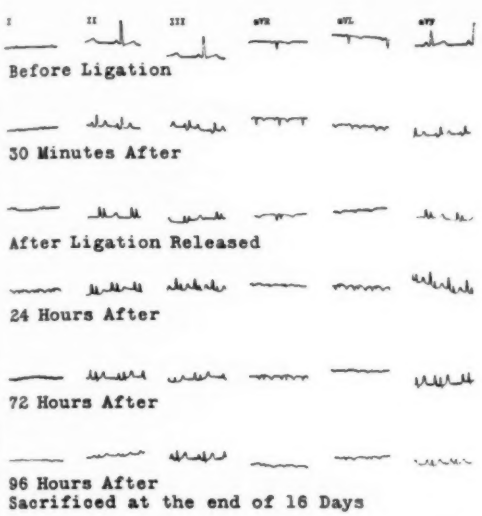

FIG. 2. Dog 43. Electrocardiogram in a case of transient occlusion of the portal vein in which the existence of signs of injury is shown.

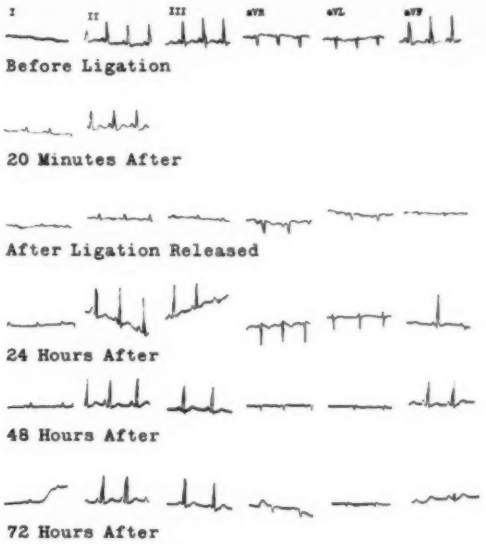

FIG. 3. Dog 46. Electrocardiogram in a case of transient occlusion of the portal vein in which only signs of subendocardial ischemia are shown.

infarct and a concordance between electrocardiographic changes and variations of the enzyme in the blood has been described. On the contrary, in the myocardial ischemia of the transient type (angina) G.O.T. levels are unchanged. In experimental coronary occlusion in the dog, an increase of 2 to 20 times of G.O.T. has been observed, but in the acute coronary insufficiency with subendocardial ischemia, blood G.O.T. changes are not so conspicuous. It is claimed that when necrosis of myocardial fibers is present the increase of G.O.T. in the blood is in accordance with the size of the myocardial area injured. The enzyme is released into the general circulation by the dead myocardial cells.

Some of the dogs showed only signs of diffuse subendocardial ischemia without changes in the G.O.T. activity of plasma, but other animals presented a late increase of the G.O.T. blood levels coincident with the electrocardiographic signs of a late epicardial lesion, all of which points out the existence of a real myocardial necrosis.

If our results are analyzed according to the classic electrocardiographic criteria, the tracings obtained in our experiments can be interpreted as exponents of diffuse subendocardial ischemia and of epicardial lesion or necrosis of the high lateral region of the left ventricle. In view of the fact that the variations of the G.O.T. activity of the plasma closely paralleled the myocardial changes,

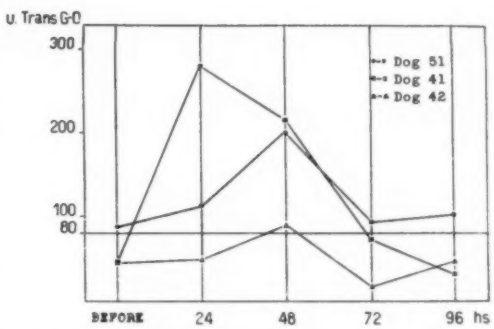

FIG. 4. Variations of plasma concentration of G.O.T. in 3 experiments of transient ligation of the portal vein. Dog 51 shows the G.O.T. plasma level increased coincident with an electrocardiographic tracing of a late myocardial infarct. In dog 42, infarct did not develop, which fact is coincident with the G.O.T. curve.

the electrocardiographic pattern has to be considered as representative of a myocardial infarct.

The fact that the late myocardial lesion appeared in the second postoperative day accompanied by an increase of G.O.T. activity of the plasma suggests the existence of factors inducing myocardial infarct which are set free after a transient circulatory derangement of the liver.

SUMMARY

1. Complete occlusion of the portal vein for 45 minutes in the dog is not followed by death. Immediately after the ligature is placed the systolic blood pressure falls abruptly to levels of between 20 to 50 millimeters of mercury followed by a slow decline. Fifteen minutes after the ligature has been released, the systolic blood pressure rises, reaching levels slightly lower than the initial values.

2. During the period of occlusion, electrocardiographic patterns of subendocardial ischemic lesions were obtained in 100 per cent of the animals. In 41.66 per cent these lesions were accompanied by patterns of ischemic epicardial lesions of the high anterolateral region of the left ventricle. The ischemic epicardial lesion persisted in the course of the subsequent days with slight variations of electrocardiographic intensity.

3. In 33.3 per cent of the animals it was observed during the following days that the subendocardial ischemia almost disappeared, and a normal electrocardiogram was obtained at the end of the second postoperative day. In 25 per cent of the animals an accentuation of the subendocardial lesion was registered in the second postoperative day, and in 16.6 per cent of the cases signs of a late ischemic epicardial lesion appeared in the electrocardiogram.

4. Increased activity of G.O.T. of plasma closely paralleled the electrocardiographic changes. It is concluded that, in 58 per cent of the cases of experimental portal occlusion of a 45 minute period, a myocardial lesion is produced which has all the characteristics of a myocardial infarct of the high anterolateral region of the left ventricle.

5. The transient complete occlusion of the portal vein during a period of 45 minutes in the dog is a simple experimental procedure to induce a type of myocardial ischemic necrosis with an electrocardiographic pattern and humoral changes similar to the myocardial infarct found in human beings. We suggest the existence of factors inducing myocardial infarct which are set free after a transient circulatory derangement of the liver.

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COAGULATION CHANGES IN EXPERIMENTAL PHLEBOTHROMBOSIS

HECTOR M. MARIN, M.D., MARIO STEFANINI, M.D., Ph.D.,
RAUNO HEIKINHEIMO, M.D., and FRANCO SOARDI, M.D., Boston, Massachusetts

IN THE FIRST ARTICLE of this series (3), it was confirmed that, in dogs, the association of stasis and of temporary blood hypercoagulability induced by the intravenous injection of homologous serum results in the formation of a venous thrombus in the area of stasis, even in the absence of appreciable lesions of the intima. Once formed, the thrombus continues to propagate until the venous segment undergoing thrombosis is completely occluded. In the present article, the chronologic coagulation changes are described which occur in a partially isolated but not occluded vascular segment during the formation and the propagation of a thrombus as compared with the status in the general venous circulation. Changes in the fibrinolytic system will be described subsequently (8).

MATERIALS AND METHODS[1]

A total of 60 dogs was used. Dogs were fed Purina biscuits and water ad libitum before and during these studies. This number does not include animals used in preliminary work, when blood samples were collected by percutaneous femoral vein puncture in nonanesthetized dogs, to study the influence of anesthesia on the blood clotting mechanism. Both femoral and jugular veins were exposed under pentothal anesthesia. Segments of the jugulars and the left femoral veins were isolated between two partially occluding ligatures by the previously described technique. The right femoral vein was left intact and samples removed from it represented blood from the general circulation. Blood samples were collected also from the areas adjacent to the stenosed segments. To obtain blood, 17 gauge needles connected to polyethylene tubes, 3 centimeters long, were inserted and blood allowed to flow freely into silicone coated test tubes. In the case of stenosed veins the rate of flow was invariably greater in the distal than in the proximal area. Needles were then removed and new ones reintroduced when further blood samples were collected. A temporary hypercoagulability was then induced with the rapid infusion of 10 milliliters per kilogram of weight of homologous canine serum. Blood samples were collected by the same method at the end of the serum infusion—15, 30, 60 minutes, and 24, 48, and 96 hours afterward. Because of the technical difficulties involved in performing multiple exposures of veins and venesections in the same dog, and also to avoid removal of excessive volumes of blood, 2 groups of animals were studied, one in the early phase and the other in the late phase, after 24, 48, and 96 hours.

Several determinations were carried out on each sample of blood. Each value given in this article represents the average in samples collected from at least 2 areas or all 3 areas at the same time. When needed, plasma and serum were diluted with veronal saline buffer, and plasma was absorbed with 100 milligrams of barium sulfate per milliliter. Simplastin was used in all determinations. Constants studied included the plate-

From the Joseph Stanton Memorial Laboratories, Saint Elizabeth's Hospital, and the Department of Medicine and Surgery, Tufts University School of Medicine, Boston.

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[1]In the course of this article, "segment above ligature" indicates the area above the ligature distal to the heart and "segment below ligature" indicates the area below the ligature proximal to the heart. "Stenosed segment" indicates the area between two partially occluding ligatures.

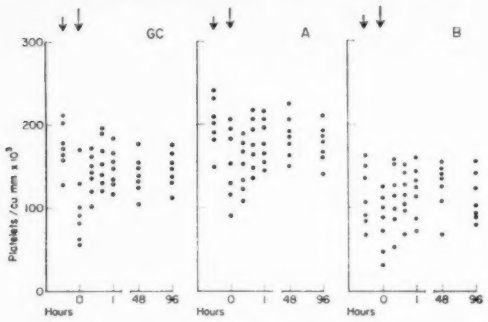

FIG. 1. Behavior of platelets before, during, and after experimental thrombus formation. GC, General circulation; A, area above stenosed segment; B, area below stenosed segment. First arrow indicates the time of application of ligatures, the second arrow indicates the end of infusion of serum. (These signs apply to all figures.) Note the fall of platelet count during the infusion of serum and the higher platelet count above the stenosed segment.

let count by a direct method, described previously (9), and the observations of the structure of platelets on smears stained with Wright's stain. The clotting time after recalcification was studied on platelet-poor and platelet-rich plasma; the generation of thromboplastin with a modification of the technique of Biggs and Douglas, using cephalin as substitute for the platelet reagent and diluting the plasma 1:25 and the serum 1:10. In other experiments, plasma or serum only was from the experimental animal and the alternate reagent was from a normal anesthetized dog. In the course of this article "generation of thromboplastin in plasma" indicates results obtained when plasma was used from the experimental animal and serum from an untreated animal; "generation of thromboplastin in serum" indicates results obtained when plasma was used from an untreated animal and serum from the experimental animal. The generation of thrombin was studied on platelet-rich plasma by a modification of the technique of Pitney and Dacie. Five-tenths milliliter of undiluted plasma was recalcified with equal volume of 0.025 molar solution of calcium chloride. One-tenth milliliter aliquots of the mixture were added at 1 minute intervals to test tubes containing dog plasma treated with barium sulfate and diluted with 2 volumes of veronal buffer. Clotting times were converted into units of thrombin by means of a standardized curve, which was experimentally prepared by plotting the clotting time of deprothrombinized plasma after addition of various units of bovine thrombin. Activity and concentration of prothrombin in plasma and serum with one and two stage techniques (9), prothrombin consumption (9), plasma fibrinogen (6), activity in plasma of Hageman (7), and of Stuart factor (1) were determined by the methods of the investigators referred to in parentheses. Activity of antihemophilic globulin and plasma thromboplastin component were calculated by standard techniques, using plasma of patients with severe forms of these diseases as substrate. The activity of stable factor (factor VII) was determined as proconvertin by Owren's method using plasma or serum diluted 1/80. The activity of labile factor (factor V) was determined by the method of Wolf using plasma diluted 1/80. In order to confirm the presence in plasma and serum of agents capable of accelerating the conversion of prothrombin to thrombin, the following technique was also used: Barium sulfate treated plasma from the experimental dog or native serum was diluted 1/80. Two-tenths milliliter of plasma or serum was then added to a freshly prepared mixture containing 0.2 milliliter of a solution of purified canine prothrombin[2] and 0.4 milliliter of simplastin. One, 2, 4, and 6 minutes after beginning of incubation, 0.1 milliliter aliquots of the mixture were then transferred to test tubes containing 0.1 milliliter of a solution of bovine fibrinogen in

[2]To prepare purified canine prothrombin, oxalated plasma was treated with barium sulfate (25 mgm./ml.). The mixture was incubated at 37 degrees C. for 15 minutes with frequent agitation and then centrifuged. The supernatant was discarded. The sediment was washed 3 times with acetate buffer (0.02 M, p_H 5.2) at room temperature and then dissolved in a 5 per cent sodium citrate solution in physiologic saline. The final volume equalled that of the original plasma. After additional centrifugation for 10 minutes, the supernatant was dialyzed overnight against water at 4 degrees C., lyophilized and stored at 4 degrees C. At the moment of use, a solution was prepared containing 1 milligram of material in 1 milliliter of veronal saline buffer.

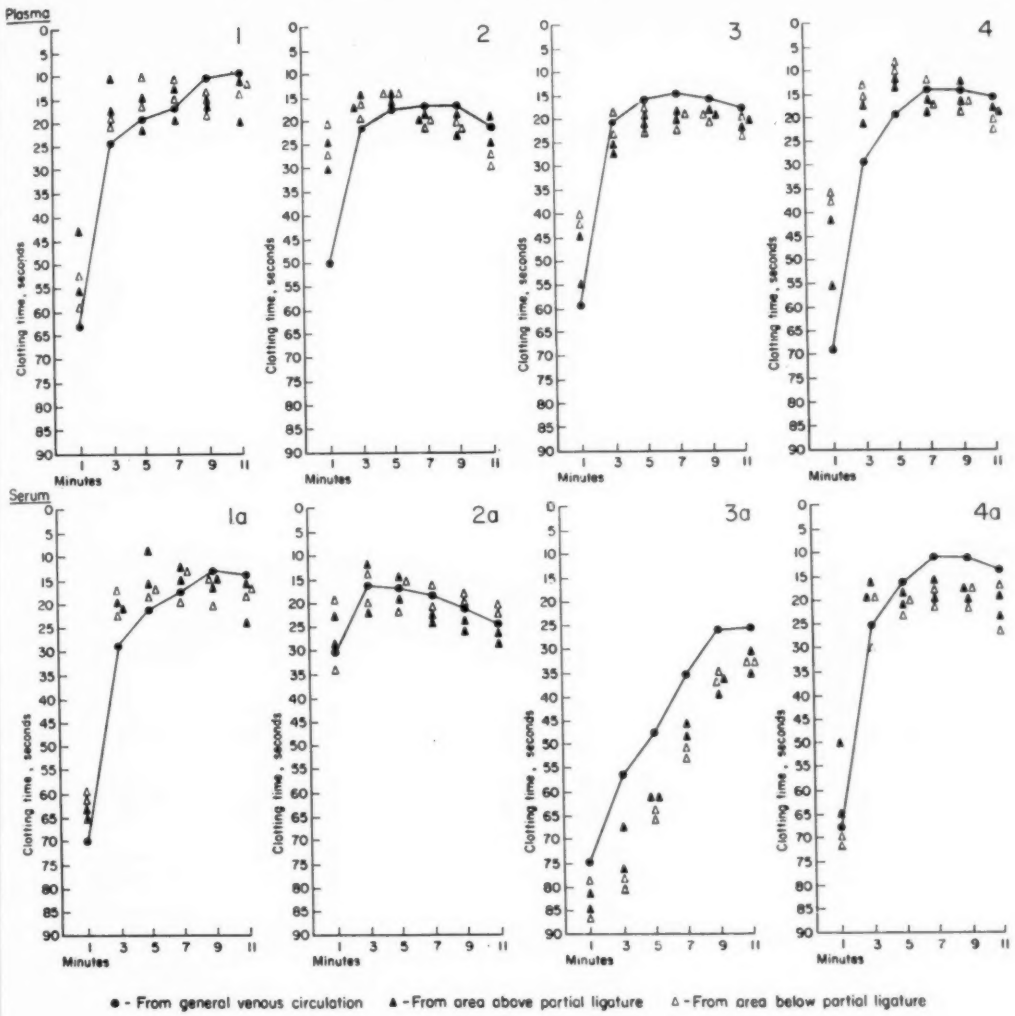

FIG. 2. The generation of thromboplastin in plasma and serum before, during, and after an experimental thrombus formation. 1, After application of ligatures: moderate increase in the generation of thromboplastin in proximity of the stenosed segments. 2, End of infusion of serum: marked acceleration of generation of thromboplastin in plasma and especially in serum in all segments. 3, Thirty minutes later: marked deceleration of the generation of thromboplastin in serum. Note slight acceleration in proximity of the stenosed segment when plasma was used. 4, Forty-eight hours later; persistent acceleration of the generation of thromboplastin from areas close to thrombosing segments, evident especially when plasma from the experimental dog was used. Results with both plasma and serum from the experimental animal are very similar but less striking than those observed when "serum" from the experimental dog was used. Therefore, they are omitted for clarity's sake. In the same figure "plasma" means results with plasma from experimental animals and normal serum. "Serum" means results with serum from experimental animals and normal plasma.

TABLE I.—GENERATION OF THROMBOPLASTIN DURING THROMBUS FORMATION (ALL DATA ARE BASED ON RESULTS IN 6 ANIMALS)

(a) Plasma and serum reagents from the experimental animal

Incubation time (min.) of reagents for TGV	*After partial ligature*	*Time after infusion of serum*				
		0	*30 min.*	*1 hr.*	*48 hrs.*	*96 hrs.*
		(SECONDS)				
		GENERAL CIRCULATION				
1	44.3±7.2	18.2±2.0	49.1±8.2	44.4±8.2	35.1±6.0	36.3±5.0
3	16.2±2.0	13.3±1.5	20.0±2.0	18.3±2.5	17.7±1.0	16.1±1.0
5	13.1±1.5	14.4±1.0	14.4±1.3	13.2±1.0	14.1±0.5	14.0±1.0
7	13.2±0.7	18.1±0.5	14.6±2.0	13.4±0.4	14.0±0.4	14.4±0.4
9	18.0±1.2	20.5±2.0	24.8±3.2	21.5±1.0	24.9±1.6	19.8±1.2
11	28.4±3.0	30.6±4.3	32.0±2.4	30.6±3.2	32.8±2.3	28.7±2.0
		ABOVE STENOSED SEGMENT				
1	38.5±6.0	18.3±3.0	49.1±12.0	50.4±9.0	30.3±8.0	38.5±4.0
3	14.3±1.0	14.3±1.0	15.3± 0.5	19.3±1.0	17.4±1.5	18.6±1.0
5	13.0±1.5	16.4±0.5	15.4± 0.3	13.2±0.5	13.6±0.5	14.8±0.4
7	13.0±1.0	19.1±0.7	18.5± 1.2	13.1±0.2	14.7±1.0	15.5±0.1
9	19.3±2.0	21.2±1.2	24.6± 2.0	20.0±1.3	18.4±1.3	21.2±1.5
11	24.4±3.1	34.3±3.1	30.8± 4.3	32.1±3.2	28.3±2.4	32.3±3.2
		BELOW STENOSED SEGMENT				
1	36.3±5.0	16.5±5.0	46.8±11.0	49.0±6.5	29.3±5.0	28.3±6.5
3	15.2±1.0	14.3±1.0	16.7± 1.5	17.4±1.0	18.0±1.0	19.5±1.0
5	13.1±0.4	13.1±0.5	14.5± 0.1	13.7±0.2	14.5±0.1	14.6±0.2
7	13.0±0.5	18.0±0.1	14.2± 0.5	14.5±0.5	13.4±0.5	14.8±0.4
9	18.0±1.0	24.0±2.2	18.1± 1.2	19.1±1.0	18.1±1.2	21.7±1.0
11	29.4±2.3	28.1±3.0	31.2± 2.1	28.2±2.1	30.0±2.3	33.1±3.1

(b) Normal serum and plasma from the experimental animal

Incubation time (min.) of reagents for TGT	*After partial ligature*	*Time after infusion of serum*				
		0	*30 min.*	*1 hr.*	*48 hrs.*	*96 hrs.*
		(SECONDS)				
		GENERAL CIRCULATION				
1	43.2±6.0	43.2±4.5	40.1±7.0	40.2±9.3	44.3±8.0	48.0±12.2
3	16.7±1.3	15.4±2.0	18.0±3.5	16.0±3.0	17.2±2.4	16.2± 3.4
5	13.1±1.0	14.5±1.0	14.2±1.0	14.1±0.5	13.4±1.0	14.4± 2.0
7	13.0±0.5	13.1±0.5	14.4±1.5	14.0±1.0	12.0±0.7	14.0± 1.0
9	17.2±1.0	18.0±2.0	16.7±2.4	16.3±2.0	15.8±3.2	18.1± 2.5
11	22.3±2.0	24.2±3.5	26.8±3.0	24.1±4.5	26.1±4.7	24.0± 2.5
		ABOVE STENOSED SEGMENT				
1	36.3±5.5	32.5±4.1	38.5±6.0	31.4±6.3	30.5±3.0	31.0±6.5
3	14.4±1.0	13.6±0.5	14.4±2.0	14.3±0.5	14.6±1.0	16.1±2.0
5	13.8±0.5	13.8±1.0	14.1±1.0	13.1±1.0	14.1±0.5	14.0±1.0
7	13.1±1.0	15.1±0.5	15.0±1.0	13.0±0.4	14.3±1.0	14.3±0.5
9	18.0±0.5	21.8±2.0	18.0±2.0	16.5±1.0	18.5±2.0	20.4±2.0
11	27.8±3.4	30.0±3.0	28.2±2.5	30.7±4.0	27.6±3.0	31.1±3.0
		BELOW STENOSED SEGMENT				
1	39.5±7.0	30.3±4.3	37.5±4.2	32.3±7.8	30.3±4.0	37.1±6.2
3	13.2±1.0	13.5±0.5	14.3±1.0	15.4±1.0	15.0±1.0	17.1±2.0
5	13.1±0.2	13.1±0.2	14.4±0.4	13.6±0.4	14.1±0.4	13.0±0.5
7	16.0±1.0	16.3±1.0	17.1±0.7	13.8±0.2	14.3±0.7	13.4±0.8
9	18.2±2.5	24.1±1.5	21.0±1.0	18.1±2.0	19.4±2.0	20.9±2.0
11	30.3±4.4	31.0±3.0	27.1±9.0	31.0±4.0	30.7±4.0	29.1±4.0

TABLE I.—GENERATION OF THROMBOPLASTIN DURING THROMBUS FORMATION (ALL DATA ARE BASED ON RESULTS IN 6 ANIMALS)—Continued

(c) Normal plasma and serum from the experimental animal

Incubation time (min.) of reagents for TGT	*After partial ligature*	*Time after infusion of serum*				
		0	*30 min.*	*1 hr.*	*48 hrs.*	*96 hrs.*
		(SECONDS)				
		GENERAL CIRCULATION				
1	45.0±7.0	16.1±2.5	58.0±13.4	48.8±6.0	47.3±8.5	40.2±7.2
3	17.2±2.0	11.3±1.4	20.0± 3.0	18.7±3.1	19.2±2.5	18.1±2.0
5	13.4±1.0	15.4±3.0	14.2± 1.0	13.1±1.0	14.4±1.0	14.5±1.0
7	13.5±0.5	14.5±1.0	14.4± 1.5	13.2±1.0	14.5±0.5	13.8±0.5
9	19.7±2.0	14.0±0.5	16.6± 2.0	18.1±2.0	19.7±2.0	19.1±1.0
11	26.1±3.4	24.1±2.0	28.8± 3.5	26.0±3.0	28.8±3.7	26.0±2.0
		ABOVE STENOSED SEGMENT				
1	36.5±8.0	15.6±1.0	59.1±12.0	41.8±6.0	46.2±3.0	36.5±5.0
3	15.3±2.0	11.1±2.0	24.3± 2.0	19.1±3.0	18.3±1.0	19.3±1.0
5	13.4±1.0	15.3±2.0	18.2± 1.0	16.9±1.0	15.5±0.5	15.4±0.5
7	13.1±0.5	15.1±1.0	20.5± 2.0	16.0±0.5	15.8±1.0	15.1±0.3
9	19.0±2.0	19.0±3.0	24.7± 3.0	25.0±2.0	20.9±2.0	21.0±1.0
11	27.0±3.0	32.3±4.0	35.9± 6.0	30.3±3.0	30.2±4.0	28.0±3.0
		BELOW STENOSED SEGMENT				
1	40.5±8.0	16.5±2.5	62.0±13.7	44.4±8.7	40.1±4.3	39.1±4.5
3	16.2±2.0	12.7±1.0	26.2± 3.0	20.5±2.0	19.0±1.0	18.5±1.0
5	13.4±0.5	15.9±0.5	16.3± 0.5	15.7±0.5	14.1±0.5	18.7±0.7
7	13.6±0.3	16.1±1.0	16.2± 1.0	15.1±0.3	14.1±1.0	20.0±2.0
9	21.0±2.0	21.0±2.0	24.0± 3.0	26.0±2.0	23.2±2.0	24.9±2.5
11	30.1±4.6	31.0±3.0	36.5± 3.5	34.6±4.0	32.5±3.0	31.8±4.5

veronal buffer—1 milligram per milliliter. Clotting times were recorded. As this represented a qualitative test evaluating the speed of conversion of prothrombin, results were expressed as clotting time in seconds rather than in units.

Antithrombin activity of plasma was studied according to a standard technique. Antithromboplastic activity was evaluated by 2 different techniques, using native serum from the experimental animal. In one technique, 0.1 milliliter of undiluted serum was mixed with 0.2 milliliter of simplastin in test tubes kept in water bath at 37 degrees C. One-tenth milliliter of 1/10 diluted normal platelet-poor dog plasma was added immediately or after 30 minutes of incubation. The difference in clotting time was taken to represent activity against tissue thromboplastin.

In another technique, 0.1 milliliter of serum was added to 0.9 milliliter of 1/10 diluted platelet-poor dog plasma and the mixture was recalcified with 1 milliliter of 0.025 molar solution of calcium chloride. After a clot formed, it was incubated at 37 degrees C. for 1 hour. Then, the clot was removed around a glass rod and the residual prothrombin determined by a standard technique. This test possibly represented a measurement of the activity of the dog serum against plasma thromboplastin.

Mechanical and osmotic fragility of the red cells was determined by standard methods.

RESULTS

Pentothal anesthesia. Under our experimental conditions, the effects of successful and uneventful anesthesia were negligible.

Stasis. There were no significant changes in the blood from the general circulation, but obvious ones were evident in the areas proximal and distal to the stenosed segment. Above the segment, the platelets (Fig. 1) were slightly increased in number

TABLE II.—SPEED OF CONVERSION OF PURIFIED PROTHROMBIN BY ABSORBED PLASMA OR SERUM FROM VARIOUS AREAS OF DOG WITH EXPERIMENTAL VENOUS THROMBOSIS

Reagent added to the prothrombin and simplastin mixture	*Incubation time of mixture*	*After partial ligature*	*Time after infusion of serum*			
			0	*1 hr.*	*48 hrs.*	*96 hrs.*
		SECONDS				
Veronal buffer	1	131.2±18.0	121.8±14.0	141.6±17.0	130.5±21.0	150.5±24.0
	2	53.4± 5.0	48.5± 4.0	50.5± 7.0	52.4± 8.0	50.6± 9.0
	4	40.2± 6.0	37.4± 5.0	39.0± 4.0	41.5± 4.0	37.6± 3.0
	6	20.3± 2.0	21.3± 1.0	20.5± 2.0	20.5± 1.0	20.4± 1.0
Plasma from the general circulation	1	75.4±10.0	34.5± 8.0	68.5±11.0	72.5±10.0	64.5± 7.0
	2	25.8± 4.0	20.4± 4.0	28.4± 5.0	27.8± 6.0	21.4± 4.0
	4	20.4± 2.0	18.2± 1.0	20.5± 2.0	19.4± 2.0	21.6± 3.0
	6	18.6± 1.0	17.0± 1.0	18.1± 1.0	16.2± 1.0	18.4± 1.0
Plasma from above stenosed segment	1	77.4±11.0	23.5± 4.0	48.4±11.0	59.5± 9.0	53.4± 7.0
	2	37.4± 3.0	17.4± 3.0	18.5± 3.0	20.4± 3.0	20.5± 4.0
	4	19.5± 1.0	16.3± 1.0	14.4± 1.0	19.1± 0.5	17.3± 1.0
	6	18.4± 3.0	15.4± 1.5	13.3± 0.5	17.0± 0.3	16.4± 0.7
Plasma from below stenosed segment	1	80.8±18.0	24.4±12.0	49.7±10.0	52.4±10.0	54.5± 8.0
	2	41.4± 7.0	12.7± 3.0	20.4± 3.0	20.1± 3.0	33.4± 3.0
	4	20.5± 1.0	12.4± 1.0	19.1± 0.5	18.4± 1.0	17.5± 1.0
	6	18.4± 0.5	18.3± 0.4	14.3± 0.8	17.5± 0.5	17.5± 0.4
Serum from the general circulation	1	89.4±11.0	67.5±10.0	88.4±10.0	80.4± 9.0	84.6±12.0
	2	30.5± 7.0	30.4± 5.0	34.5± 4.0	30.6± 4.0	38.4± 3.0
	4	20.0± 1.0	20.3± 1.0	22.6± 1.0	21.0± 1.0	20.5± 1.0
	6	16.0± 0.7	18.0± 0.2	17.0± 0.4	18.5± 0.3	19.5± 0.3
Serum from above stenosed segment	1	94.5±14.0	51.5±12.0	68.0±10.0	69.5±18.0	64.5±12.0
	2	33.7± 5.0	21.4± 3.0	30.4± 5.0	28.4± 6.0	30.7± 2.0
	4	20.0± 1.0	20.1± 0.5	19.0± 1.0	19.3± 0.5	20.0± 1.0
	6	18.2± 1.0	16.4± 0.4	19.5± 0.7	19.4± 0.7	20.5± 0.8
Serum from below stenosed segment	1	90.5±20.0	54.1±18.0	61.5±12.0	67.6± 9.0	68.7±10.0
	2	30.4± 4.0	20.4± 4.0	30.4± 4.0	25.6± 3.0	27.5± 3.0
	4	20.4± 1.0	19.5± 0.5	19.0± 1.0	20.0± 1.0	18.3± 0.5
	6	18.0± 0.4	12.6± 0.7	19.0± 0.3	16.7± 0.3	19.0± 0.3

Data are based on results in 6 animals.

possibly because of the effect of stasis, but their structure appeared unchanged. The clotting time of recalcified plasma was unmodified, yet plasma and serum contained accelerators of the generation of thromboplastin (Fig. 2 and Table I). Essentially the same changes were noted in the blood from the area below the stenosed segment, with two significant exceptions: the number of platelets was relatively decreased (Fig. 1), and the clotting time of recalcified plasma (Fig. 3) was slightly prolonged. It was also noted that the rate of thrombin formation was not accelerated, although its total yield was greater in the blood from below the stenosed segment (Fig. 4).

Temporary hypercoagulability. The infusion of serum had striking effects on the coagulability of the blood from both the general and local circulation. Changes in the same direction were noted in the general circulation and in the area above the stenosed segment. The number of platelets fell. They appeared clumped and numerous dendrites were seen on stained smears. The clotting time of recalcified plasma was unchanged. The activity of the labile factor (Fig. 5) decreased and that of stable factor (Fig. 6) increased in plasma and more so in serum. The generation of thromboplastin was markedly accelerated, especially at the peak of infusion and shortly thereafter, and when the serum from the experimental dog was used (Fig. 2 and Table I). The generation of the thrombin was also accelerated (Table II). The same changes were observed in blood from below the stenosed segment. In addition, the recalcified clotting time of platelet-rich and of platelet-poor plasma became very close. Also, the number of platelets was lower below than above the stenosed segments. The two results may in-

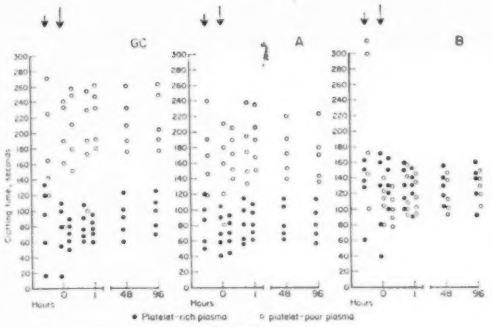

FIG. 3.

FIG. 3. Clotting time of recalcified platelet-rich and platelet-poor plasma before, during, and after experimental thrombus formation. The clotting time of recalcified platelet-rich plasma from below the stenosed segment is prolonged; yet that of platelet-poor is shorter and similar to that of platelet-rich plasma.

FIG. 4. Generation of thrombin before, during, and after experimental thrombus formation. 1, After application of ligatures: increased generation of thrombin in blood leaving the stenosed segments. 2, At the end of infusion of serum: rapid acceleration and higher yield of all samples. 3, Thirty minutes after infusion: persistent acceleration in blood from thrombosing segment. 4, Forty-eight hours later: similar trend, although the magnitude of the effect is less striking. The continuous line represents results in blood from the general circulation. The other points indicate 3 experimental results using blood leaving the thrombosing segment.

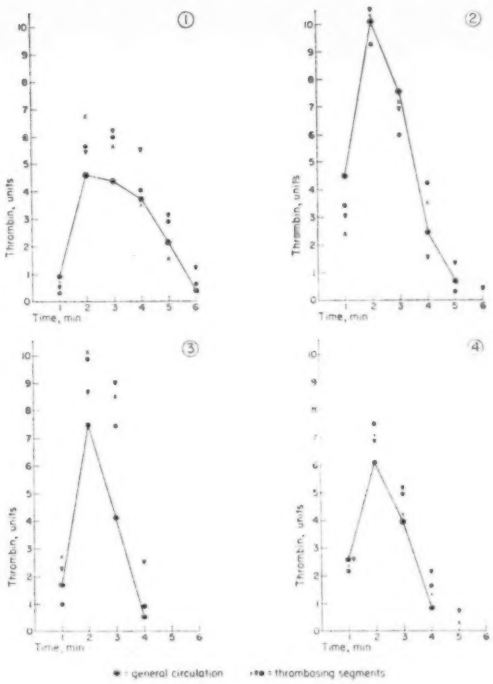

FIG. 4.

dicate that platelets were used within the thrombosing segment, releasing their thromboplastic factors. Finally, the formation of thrombin was also accelerated but its yield was not greater than in blood from the general circulation (Figs. 4 and 7).

Propagation of the thrombus. For the purpose of clarity, changes observed are described independently for each factor. No values are available beyond the 96 hour period. At this time, the circulation in the thrombosing segment was limited, and samples of blood collected below it were clearly insufficient. When blood could be collected satisfactorily, the results after 96 hours were essentially similar to those obtained at 48 hours.

Platelets remained higher in number in the area above and lower in the area below the stenosed segment when compared with the prompt return to preinfusion levels in the general circulation. Morphologic studies of platelets from the blood collected below the stenosed segment revealed considerable clumping and the presence of numerous dendrites for at least 48 hours. No such changes were evident in the platelets of blood from other areas.

The clotting time of platelet-rich plasma remained prolonged and that of platelet-poor plasma remained accelerated in blood collected below the stenosed segment for as long as 96 hours. As a result, their paradoxic similarity continued, again probably indicating sustained destruction of platelets during passage through the area of thrombosis.

The activity of stable factor(s), after reaching a peak at the time of infusion of serum, remained lower above and higher below the stenosed segment. Results, however, were not striking.

Activity of labile factor continued high in the blood taken from below the stenosed segment.

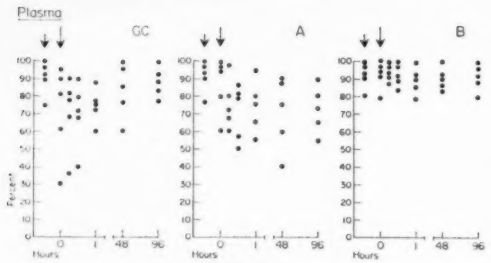

FIG. 5.

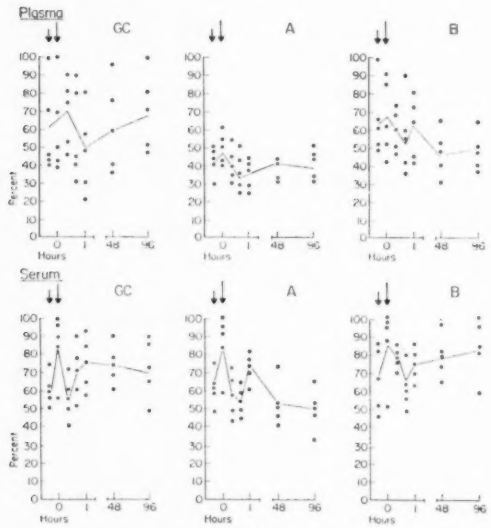

FIG. 6.

FIG. 5. Plasma labile factor activity before, during, and after experimental thrombus formation.

FIG. 6. Stable factor activity before, during, and after experimental thrombus formation.

The generation of thromboplastin was slow and incomplete in samples from all segments. This fact was strikingly evident when normal plasma and serum from the experimental dog were used. A tentative explanation of these findings may be seen in the discussion of the behavior of antithromboplastin.

A most striking phenomenon following the infusion of serum was a marked increase in the yield of thrombin in all segments. This was still observed only locally for at least ½ hour after the infusion of serum. The effect was still appreciable 48 hours later.

Behavior of other clotting factors and miscellaneous observations. There were no significant changes at any time in the activity of antihemophilic globulin, plasma thromboplastic component, Hageman factor, and Stuart factor. It was noted that dog's plasma was very rich in antihemophilic globulin and rather deficient in plasma thromboplastic component, with wide variations between one animal and another. Determinations of prothrombin activity and concentration by one and two stage methods and determination of residual prothrombin activity in serum by the prothrombin consumption test did not yield any significant results. The variations in fibrinogen were inconsistent and, at times, contradictory, which may well reflect the inadequacy of the available methods for the determination of this protein.

The effect of absorbed plasma and of native serum obtained from the local segments as well as from the general circulation on the speed of conversion of partially purified prothrombin was also studied at various intervals of time. Stasis did not appear important. After the infusion of serum, however, the plasma or serum from the segments close to the area of thrombosis accelerated the conversion of prothrombin to a greater degree than samples from the general circulation (Fig. 7). The phenomenon was still evident 48 hours later. It was abolished when either the plasma or the serum was stored overnight at 37 degrees C. (Fig. 8).

There was no indication that any antithrombin activity developed. No inhibitor of plasma thromboplastin was found by the prothrombin consumption technique. The incubation of the experimental dog serum with tissue thromboplastin, on the other hand, indicated that antithromboplastin activity had developed in the general circulation and in the area above the thrombosing segment at the time of infusion of serum. It was demonstrable for 30 minutes or so. In the area below the stenosed segment the antithromboplastin activity was much evident after 30 minutes and continued for at

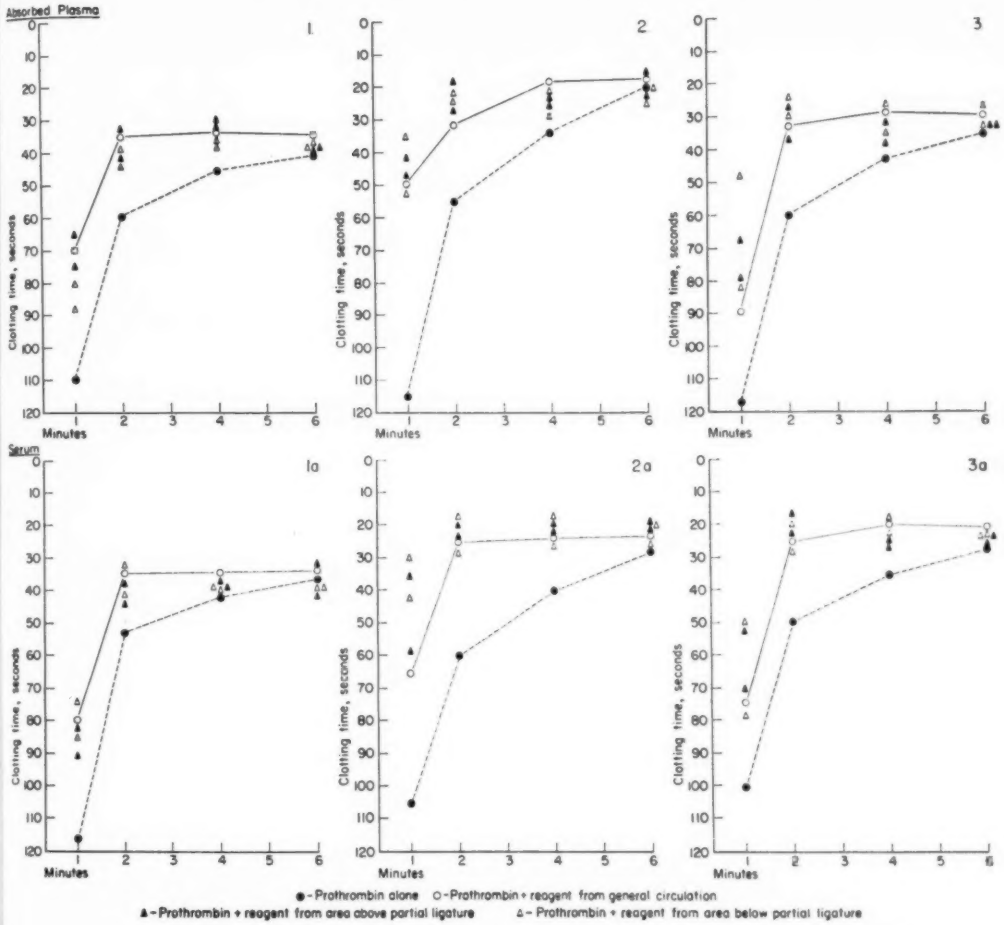

FIG. 7. Effect on the conversion of prothrombin to thrombin of absorbed plasma and serum from samples of blood collected before, during, and after experimental thrombus formation. Broken line represents self-activation of the admittedly grossly contaminated preparation of prothrombin. 1, After application of ligatures: stasis does not affect the speed of prothrombin conversion. 2, End of infusion of serum: acceleration is seen in samples from all areas. 3, Forty-eight hours later: acceleration continues in samples from above and below the stenosed segments. Results after 1 minute of incubation seem to indicate most significantly the acceleration in prothrombin conversion.

least 2 hours (Fig. 9). The antithromboplastin activity was much less evident in plasma than in serum, a result which defies interpretation at this time. These findings may help to explain why the generation of thromboplastin was poor in all segments 30 minutes after the initiation of the thrombus when the serum from the experimental animal was used with normal plasma, but this was not so evident when normal serum and plasma from the test animal were used.

There were no important changes in either the osmotic or the mechanical fragility of the red cells.

DISCUSSION

In the analysis of the pathogenic mechanisms of venous thrombosis, a differentiation

should be made between the initial formation and the propagation of a thrombus. The experiments reported in this article may help to clarify both phases, and especially the phase of propagation of the thrombus. In the absence of demonstrable vascular injury, the initiation of clotting responsible for the formation of a thrombus was triggered in our studies by the combined effect of stasis and of temporary hypercoagulability of the blood. Their effects appear complex to analyze. Stasis undoubtedly caused slowing of blood flow, anoxia of the vascular wall and this, in turn, might have led to changes in the intima which, although not demonstrable, were possibly present in our animals. Furthermore, stasis is known to cause shifting of platelets from the center to the periphery of the blood stream. In our experiments, stasis probably accounted for the increased platelet count above the stenosed segment. Yet, stasis alone had no significant effect on the blood clotting mechanism in the general circulation or on the speed of thrombin formation at the level of the stenosed segment. Apparently, more important in the initiation of the thrombus was the state of hypercoagulability induced by the injection of serum. The changes observed in the general circulation as well as in the stenosed segment were indicative of increased speed of formation, of higher yield of thrombin, and of over-all acceleration of the coagulation process. These changes seemed to coincide with the initiation of thrombosis, and then sudden hypercoagulability of blood might have been the precipitating mechanism in the formation of a venous thrombus in the presence of favoring mechanical factors. Some attention has been given to platelets in the mechanism of initiation of thrombosis. Their role is controversial. Either platelets precipitate on the intima as the first step of thrombus formation and their disintegration initiates clotting, or their precipitation is due to the effect of thrombin, initially formed from prothrombin through mechanisms which are uncertain at present. Our experiments did not help to clarify this controversy, although, as further discussion will indicate, platelets undoubtedly played an early and important role in the propagation of the thrombus.

In evaluating the conditions which induced the propagation of the thrombus, it is obvious that the complex changes observed at the level of thrombus formation were influenced by several factors. Blood coagulation factors are utilized in the clotting process and become converted to more active agents which greatly accelerate the process of coagulation and, presumably, of intravascular clotting. Anticoagulants may also develop, and the fibrinolytic system may be activated in the course of intravascular coagulation. Our experiments, in fact, showed the appearance of an anticoagulant and the activation of the fibrinolytic system, although fleetingly, during the phase of initiation and in the early phase of propagation of the thrombus (8). With due consideration of these variables, the analysis of the changes occurring at the level of a venous segment while a thrombus was propagating focused attention on the platelets and on the labile factor. The behavior of the two agents, in turn, influenced the over-all behavior of the clotting time of recalcified plasma and of the generation of thromboplastin and thrombin which were faster at the local level as long as the thrombus continued to extend. The number of platelets remained high above and low below the stenosed segment. At the same time, the clotting time of recalcified platelet-poor plasma was short, and little difference was found between clotting time of platelet-rich and of platelet-poor plasma collected below the stenosed segment. The rapid clotting time of platelet-poor plasma probably indicated disintegration of platelets and release of their thromboplastic material. The persistently increased activity of labile factor in the plasma collected below the stenosed segment also seemed important. The identification of the accelerating agent(s) with the labile factor was based on the observation

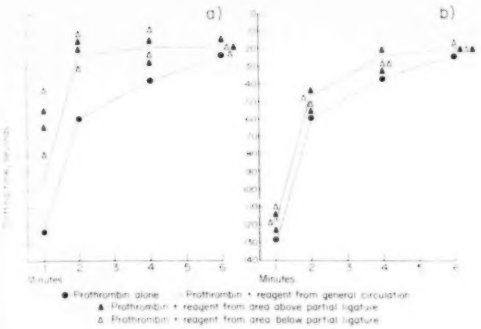

FIG. 8.

FIG. 8. Effect of storage on the ability of absorbed plasma from experimental dog, taken 48 hours after initiation of thrombosis, to accelerate the conversion of prothrombin. a, Fresh plasma. b, Plasma stored at 37 degrees C. overnight.

FIG. 9. Inhibitory activity on tissue thromboplastin of serum during experimental thrombus formation.

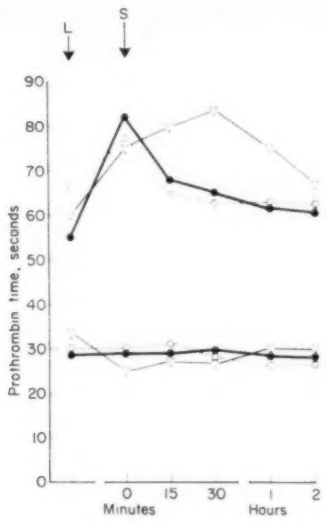

FIG. 9.

that they disappeared rapidly upon storage. The importance of these two agents was further emphasized by a surprising lack of appreciable variations in other plasma agents which are known to be essential to the formation of the clot. Thus, no significant changes were found in the plasma level or activity of antihemophilic globulin, plasma thromboplastic component, prothrombin, Stuart factor, Hageman factor, and fibrinogen. Several reasons for these findings may be advanced. First, not enough is known of the clotting mechanism in the dog to appreciate whether it is essentially similar to that in man; thus, antihemophilic globulin and labile factor are present in large excess in dog plasma, while plasma thromboplastic component is low. Also, changes in fibrinogen and prothrombin may be too subtle to be detected by our fairly insensitive methods. Finally, coagulation in vitro and in vivo differ in at least one major respect. In vitro, clotting factors are consumed and cannot be replaced. In vivo, plentiful supply is available as long as there is continued circulation of blood within the segment undergoing thrombosis. Coagulation factors are not depleted and the process of intravascular thrombosis continues indefinitely or, as in our experiments, until the segment has become totally thrombosed. It is of course significant that platelets and labile factor are two of the agents most closely involved in the autocatalytic-like reaction of blood coagulation.

A very interesting fact was brought out by the analysis of the generation of thromboplastin. This was greatly delayed and poor in the early phase of propagation of the thrombus when plasma from a normal dog and serum from the experimental animal were used as reagents. This was a paradoxic result in view of the abundant evidence of intravascular clotting and of the development of accelerators of coagulation. Without presenting details already discussed in the section on results, the phenomenon seemed tied to the appearance of a fleeting antithromboplastic activity in serum, as also seen in other instances of sudden intravascular clotting. It is of interest that the antithromboplastin was found for a longer period below the area of thrombus formation, indicating that the body may have tried to utilize the antithromboplastin against further extension of the clot, appar-

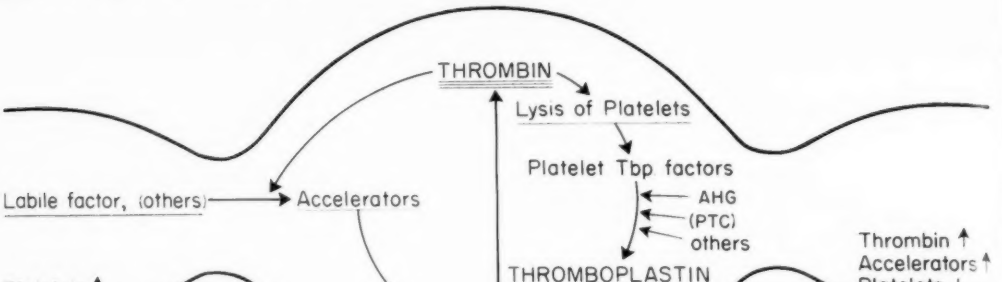

FIG. 10. A hypothesis of the dynamic mechanisms involved in the propagation of the thrombus. Arrow indicates direction of blood flow. Formation of thrombus causes activation of labile factors to accelerators of the conversion of prothrombin and lysis of platelets in the presence of plasma factors. The results are: (1) faster production of thromboplastin and thrombin; (2) continued deposition of platelets and fibrin within the segment; (3) differences between inflowing and outflowing blood, reflecting these changes.

ently without much success. There were no changes in antithrombin. The finding was not surprising as dog plasma contains huge excess of this anticoagulant.

There were no significant changes in the general venous circulation as the thrombus propagated. This fact has possibly important clinical complications. Much effort has been spent to detect thrombosis in man through changes in blood clotting factors. Findings have been described from time to time in patients suffering from thromboembolism, such as thrombocytosis, increased platelet adhesiveness to glass, shortened clotting time in siliconized test tubes, increased resistance to heparin, increased circulating antithrombin, changes in the level and reactivity of fibrinogen, and temporary increased activity of the convertin complex. These findings have been far from constant, and their application to the clinical detection of "thrombotic states" has given contradictory results. Our work suggests the futility of studying blood from the general circulation to detect intravascular clotting in local districts, possibly because of the inadequacy of the laboratory methods currently employed. Nevertheless, our experiments indicated that the only changes detected in the general circulation were found during or shortly after the infusion of serum. One could perhaps detect similar changes in man if the blood were collected at the time when thromboplastic substances were entering the circulation and thrombus formation beginning. Otherwise, the propagation of a clot continues without any significant changes in the blood collected from areas remote from the thrombosing segment. By the same token, the appreciation of the effects of anticoagulant therapy are based on changes found in the circulating blood. These, however, may not indicate reliably what goes on at the level of thrombosis. This point may interpret otherwise unexplained failures in the treatment of thromboembolic diseases.

A few comments are necessary regarding the applicability of these findings to human pathology. Reservations have already been mentioned. Yet, many similarities are obvious. In man, stasis easily occurs, especially

in elderly patients when valves are insufficient and vein walls are deformed. Hypercoagulability may develop in patients undergoing some types of surgery, during delivery, after severe trauma, and in a few medical states (such as pancreatic carcinoma) in which the common denominator is the interruption of the barrier between tissue spaces and circulatory system and entrance into the circulation of tissue thromboplastins. Hypercoagulability then determines the occurrence of thrombosis, but its site is dependent on the local mechanical factors. This should not be confused with the results of intravascular seeding of massive amounts of thromboplastin, as it may be done experimentally or may occur in abruptio placentae or amniotic embolism. Here, massive and diffuse intravascular clotting ensues even in the absence of stasis with defibrination and paradoxic hemorrhage because of massive depletion through consumption of many of the factors of clotting.

In conclusion, it would appear that the entrance in the blood stream of preformed accelerators of the formation of thrombin such as tissue thromboplastin or stable factors of serum is most important in initiating intravascular clotting but only when stasis (and intimal injury) is present. The propagation of the thrombus is possibly a more complex mechanism, closely related to the autocatalytic reaction of blood clotting. The scheme presented in Figure 10 agrees with the known facts although alternative explanations for the phenomenon are easily possible.

SUMMARY

The formation of a thrombus which propagates until the venous segment is completely occluded follows the injection of homologous serum in dogs after partially occluding ligatures have been applied to a major vein. This technique allows the study of the changes in the various clotting factors and mechanisms which accompany the initiation and propagation of a venous thrombus and their relative importance in these processes.

Stasis alone causes faster generation of thromboplastin but does not appreciably affect the speed of generation of thrombin. The infusion of serum causes acceleration of clotting in all areas, best indicated by a fall in the platelet count and in the activity of all other coagulation factors considered with the concomitant development of powerful accelerators of the generation of thromboplastin and of thrombin (temporary hypercoagulability with intravascular clotting).

Significant changes are found predominantly in the blood flowing from the stenosed segment while the thrombus extends. Platelets are reduced in number. They are probably lysed within the thrombosing segment releasing their thromboplastic factors as there is concomitant acceleration of the recalcified clotting time of platelet-poor plasma. The activity of the labile factor is also greatly enhanced during the passage of blood through the thrombosing segment, probably because of its conversion to a powerful accelerator. Thus, the generation of thromboplastin and thrombin continue to be accelerated. Within 30 minutes after the initiation of a thrombus, an antithromboplastin appears which persists for 2 hours or so in the blood flowing from the thrombosing segment. At no time are changes found in the clotting mechanism of blood taken from the general circulation which may suggest the presence of a propagating thrombus.

These results emphasize differences in mechanisms between initiation and propagation of a venous thrombus. The entrance in the blood stream of thromboplastic or clot accelerating substances is probably most important in initiating the clotting process which leads to thrombus formation when other essential conditions are present. Platelets and labile factors seemed involved mostly in the further propagation of the thrombus. They probably act through their role in maintaining a sustained autocatalytic-like reaction of blood coagulation.

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PREINVASIVE INTRADUCTAL CARCINOMA OF THE BREAST

DANIEL A. GILLIS, M.D., MALCOLM B. DOCKERTY, M.D., and
O. THERON CLAGETT, M.D., F.A.C.S., Rochester, Minnesota

CARCINOMAS OF THE BREAST take origin from ductal epithelium or its derivatives. As one might expect, instances occur in which the pathologist has an opportunity to see epithelial alterations within ducts that must be regarded as neoplastic in nature but in which the cells have not acquired the aggressive, anaplastic, and infiltrative characteristics so commonly observed in mammary carcinoma. It is recognized that such changes may be interpreted as "early," or noninvasive, carcinoma. Exactly where this interpretation begins and where it must end are points that are not too clearly defined. This becomes a problem of some magnitude, because the subsequent clinical management of the patient may rest on such an interpretation. With the hope of further delineating from clinical, pathologic, and therapeutic points of view this particular facet of the over-all problem of mammary carcinoma, a series of carcinomas of the breast in which the tumor was confined to the ducts was reviewed.

HISTORICAL ASPECTS

Although Cheatle (5, 6), Horsley, Rodman, Bloodgood (3), and others wrote extensively on the ductal origin of mammary carcinoma, mostly prior to 1930, they had little to say on the concept of in situ lesions involving this tissue.

Bloodgood (1, 2) was extremely hesitant about diagnosing papillary and nonpapillary ductal proliferative lesions as malignant, regardless of their anaplasia, unless the walls of the involved ducts were breached. Later observations by Lewis and Geschickter uncovered metastasis in follow-up studies of patients who had received less than radical treatment for Bloodgood's (2) "comedoadenomas." By 1932, when Broders described and illustrated carcinoma in situ involving several locations, including the breast, it had become obvious to many observers that such a lesion as Paget's disease of the nipple, unaccompanied by grossly infiltrating carcinoma of the underlying breast, was actually an extensive in situ ductal carcinoma of that organ with an intraepithelial component. The situation was clarified further when Muir and Aitkenhead (12) demonstrated retrogression or healing of certain intraductal malignant lesions through fibrous engulfment.

In 1941, Muir (11) stated: "In some areas practically all the small ducts and acini are lined by malignant cells, the appearance being that of a rapidly growing adenocarcinoma; yet the cells are contained within normal boundaries. . . . No actual infiltration of stroma could be detected in various parts of the breast examined, but metastasis had occurred in the lymph glands. This, of course, simply means that the focus of infiltration in the breast had escaped observation."

In 1946, Foote and Stewart (8) listed no less than 3 noninfiltrating forms of ductal carcinoma of the breast, namely, papillary carcinoma, comedocarcinoma, and lobular in situ carcinoma. All 3 types were uncommon, and none could be diagnosed as such

From the Section of Surgical Pathology and Section of Surgery, Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

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TABLE I.—SURVIVAL IN PREINVASIVE INTRADUCTAL CARCINOMA OF THE BREAST

Period, years	*Patients*		*Lived beyond indicated period*	
	Total	*Traced*	*No.*	*Survival rate, per cent**
5	32	31	30	96.8
10	24	20	18	90.0
15	10	10	7	70.0

*Per cent of traced patients. Inquiry as of 1 January 1958. The 5 year group includes only those patients who were operated on in 1952 or earlier; the 10 year group includes only those operated on in 1947 or earlier; the 15 year group includes only those operated on in 1942 or earlier.

preoperatively. They emphasized the need for extensive studies aimed at discovering foci of stromal invasion. If the latter was present, radical mastectomy was recommended to be performed as a secondary procedure.

MATERIALS AND METHODS

Review of the Mayo Clinic files disclosed that 603 surgically excised lesions of the breast were diagnosed as comedocarcinoma from 1928 through 1955. Tumors associated with Paget's disease were discarded. Also deleted were all tumors which, on preliminary review, exhibited even minor degrees of stromal infiltration. The residue of 50 lesions was further scrutinized grossly, and many new blocks were cut for microscopic examination. Fourteen of the 50 lesions were found to be invasive on this second appraisal, and these cases were eliminated. The data in this study concern the remaining 36 cases of what might be called in situ carcinoma of the breast.

CLINICAL DATA

Two of the 36 patients were in the fourth decade of life, 15 were in the fifth decade, 11 in the sixth, 6 in the seventh, and 2 in the eighth. All the patients were women.

Symptoms.—The patients were divided into 4 groups. In the first group, the patient complained of a lump in the breast. This was the only symptom in 15 instances (42 per cent). As judged from the patients' histories, the duration of existence of the lump varied from 3 days to approximately 5 years.

A second group of 9 patients (25 per cent) complained of a discharge, usually bloody, from the nipple. The duration of this symptom varied from a few weeks to 23 years.

A third group of 5 patients (14 per cent) had symptoms of both a lump and discharge from the nipple.

The final group encompassed 6 patients (17 per cent) who had no symptoms referable to either breast. In each of these cases, operation had been advised because the physician upon general physical examination had discovered a lump.

The remaining patient did not fit into any of the groups mentioned although she complained of painful breasts. Examination revealed large pendulous breasts but no other abnormality.

Physical findings. The palpable lumps varied from tiny nodules to a large mass, measuring approximately 8 centimeters in diameter. Some were discrete, and others were less well defined; in some instances, a more or less diffuse fullness or nodularity was noted in one or more zones. Fixation of the skin, retraction of the nipple, cutaneous edema, or fixation of the lesion to deeper structures was not noted.

One patient had a large firm axillary lymph node that was the source of the presenting complaint. None of the other patients had axillary adenopathy of any clinical significance.

Examination of the breasts gave entirely normal results in 5 of the 9 patients whose only complaint was discharge from the nipple. The other 4 patients had sufficiently well localized nodularity to define the region in which the offending lesion lay; in 2 instances, pressure in this region reproduced the discharge from the nipple.

Except for the breasts, results of the general physical examination were not remarkable.

LABORATORY DATA

Initial routine examinations of the blood and urine, and posteroanterior stereoscopic roentgenograms of the thorax did not reveal

findings, in any case, that had a significant bearing upon either the final diagnosis or the treatment given.

DIAGNOSIS, TREATMENT, AND SURVIVAL

The diagnosis in all cases had been established by the microscopic examination of excised tissue. In most cases in which a lump was palpable, the lesion was first removed as an excisional biopsy, the definitive surgical procedure then being completed after the diagnosis had been made by study of frozen sections. In several instances, the breast had been removed as the primary procedure.

Radical mastectomy had been performed on 24 patients (67 per cent). In 9 patients (25 per cent), simple mastectomy had been done; in 2 patients, this had been combined with axillary dissection on the involved side. Local excision had been done in the remaining case. No operative deaths had occurred.

Survival rates for 5, 10, and 15 years are summarized in Table I.

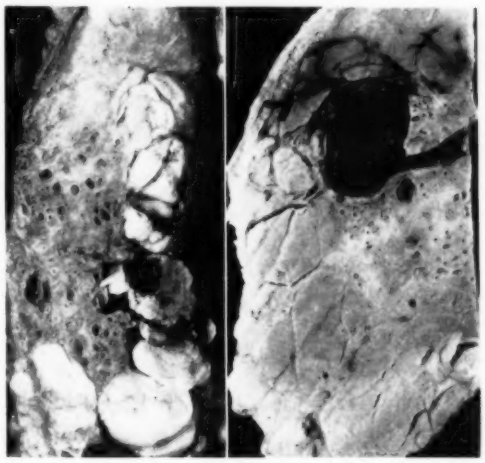
PATHOLOGIC STUDIES

Gross appearance. The tissues involved by intraductal carcinoma showed great variation, ranging from a grossly normal appearance to zones containing only a scattering of dilated ducts to zones of classic comedocarcinoma.

Intraductal carcinoma of the breast may be present over a wide expanse without producing significant alterations in the gross appearance. In such cases, the ducts have not yet undergone a sufficient degree of dilatation to make them conspicuous on gross inspection, and necrosis of tumor within the ducts has not yet occurred or is of minimal degree. This was true in several of our cases.

Alterations in gross appearance are not produced by lobular carcinoma in situ, as has been emphasized by Foote and Stewart (7, 8). The lesion is discovered incidentally during microscopic examination of excised tissue.

Some of the affected zones were surprisingly well rounded and discrete; many



a b

FIG. 1. Intraductal mammary carcinoma. a, Note dilated ducts, many of which are plugged by tumor. b, Another gross specimen showing dilated ducts containing tumor. A large simple cyst is also present.

others were ill-defined and shaded off gradually into normal breast tissue or areas of so-called chronic cystic mastitis. Varying degrees of the latter condition were encountered commonly.

Figure 1a illustrates the gross appearance of a zone of intraductal carcinoma. The obvious abnormality is the varying degree of dilatation of the ducts, many of the lumina of which are filled with plugs of tumor or the necrotic remnants of such plugs. The region of neoplasia shades off gradually into the adjacent fatty breast tissue; 1 small cyst is also present. Figure 1b depicts a less pronounced degree of ductal dilatation. The lumina of many ducts contain rather homogeneous-looking tumor tissue. Two simple cysts, 1 small and 1 large, may also be seen.

These illustrations represent the disease in an unusually advanced stage. In the presence of such extensive gross changes as those depicted, the tumor usually shows some infiltration of the mammary stroma; indeed, it appears remarkable that this is not always so. In no instance was it possible upon gross examination to be at all sure of

stromal infiltration. The fibrosing scirrhous reaction evoked by many infiltrating neoplasms was not encountered, nor were there any examples of a separate infiltrating carcinoma arising in another part of the breast.

The axillary nodes appeared to be grossly involved by tumor in only 1 specimen, and more will be said about this case subsequently. In 1 other specimen, the regional nodes were large and unusually firm, but they were free of tumor when examined microscopically. No other specimen exhibited a significant degree of axillary adenopathy. None of the patients in this series had biopsy of supraclavicular or parasternal lymph nodes.

Microscopic appearance. The cellular alterations in the affected ducts were classically widespread and were recognized rather readily. The multiplicity of affected ducts is one of the outstanding features of the disease, and it is certainly the most striking. Alterations in the stromal tissues were not remarkable.

Considerable variation occurs in the microscopic patterns presented by intraductal cancer. It is helpful for descriptive, as well as for interpretative, purposes to describe, in orderly sequence, the cellular changes occurring within the ducts from the simplest and best-differentiated tumors to the more rapidly growing lesions of a higher grade of malignancy. It is not meant to imply that this is necessarily the usual sequence of events. The following description includes all of the abnormal appearances that were encountered in this study.

The earliest detectable change from normal is proliferation of the cells lining major or minor ducts serving one or several lobules of the breast. This proliferation at first extends toward the ductal lumen, so that the proliferative process results in an ingrowth of cells that often assumes a papillary architecture within the duct. These ingrowing processes, unlike papillomas, usually are not accompanied by a well-developed stalk of connective tissue. Ordinarily, the cells at this stage are not highly atypical, and mitotic figures seldom are encountered. It is in such lesions that difficulty may arise in deciding what is benign and what should be called malignant. Figure 2a illustrates this stage of the disease, showing papillary ingrowths of slightly atypical cells without any apparent connective-tissue stalks.

As cellular growth continues, the papillary projections gradually coalesce to form a more solid intraductal tumor. As this occurs, scattered spaces remain within the lumen; this pattern of solid clumps of cells arranged around irregular spaces within the duct has been designated as cribriform intraductal carcinoma (Fig. 2b). The papillary architecture is lost by the coalescence, a greater loss of cellular polarity takes place, and the incidence of mitotic figures and cellular atypism increases. Occasionally, the spaces contain a small amount of cellular detritus or mucus. Early necrosis of the central cells within the duct may be seen, but this is not usually a feature at this stage (Fig. 2c).

As the condition progresses, the affected duct becomes practically filled with tumor cells, the ultimate formation being a solid intraductal tumor (Fig. 2d). Coincident with this are increasing anaplasia and evidence of more rapid growth. The cells show almost total loss of polarity, and mitotic figures are relatively common. With increasing rapidity and extensiveness of growth, the cells toward the center of the lumen outgrow their blood supply, and varying numbers of them undergo necrosis. This produces the classic picture of comedocarcinoma; the necrosis may be so extensive that only a thin rim of viable malignant cells remains around the periphery of the ductal lumen (Fig. 3a). Calcium is often deposited in the necrotic zones.

The final phase in the process is failure of the wall of the duct to confine the tumor to its lumen, and stromal invasion takes place (Fig. 3b). This may occur at any time after inception of the neoplastic process. The cellular pattern in the stromal tissues of the breast does not have any unusual charac-

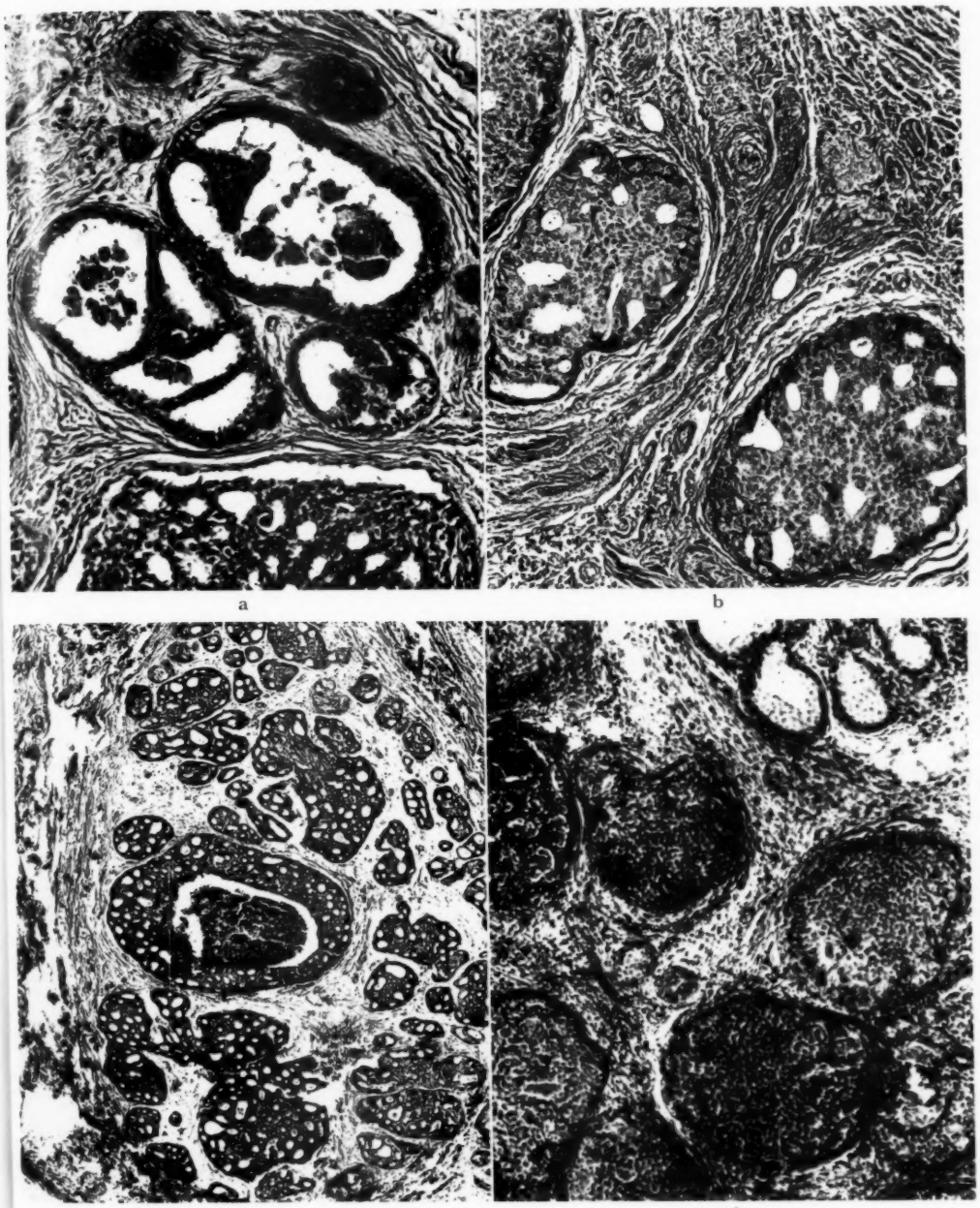


Fig. 2. Intraductal mammary carcinoma. a, Intraductal papillary ingrowths of slightly atypical cells without any apparent connective-tissue stalk. Hematoxylin and eosin, ×110. b, Cribriform pattern of intraductal carcinoma. Hematoxylin and eosin, ×110. c, Cribriform intraductal carcinoma with central necrosis in a large duct. Hematoxylin and eosin, ×44. d, Solid intraductal carcinoma. Hematoxylin and eosin, ×98.

teristics, being similar to that seen within the ducts and resembling the pattern encountered in the commoner forms of predominantly infiltrative breast carcinoma.

Zones of lobular carcinoma in situ were encountered several times in this series in association with intraductal carcinoma involving the larger ducts. In such lesions, the affected lobules were enlarged, and their normal architecture was distorted. These in situ tumors showed noninfiltrative cellular proliferation, with moderate hyperchromasia and nuclear atypism, loss of polarity, reduction or obliteration of the acinar lumina, and scattered infrequent mitotic figures (Fig. 3c and d).

Fibrous and elastic thickening of the walls of ducts, with apparent engulfment of tumor cells, was seen only infrequently.

The degree of malignancy in these 36 carcinomas was grade 1 in 12, grade 2 in 15, mixed grades 1 and 2 in 2, grade 3 in 6, and grade 4 in only 1. Thus, 29 of the 36 lesions (80 per cent) were grade 1 or 2. The single grade 4 carcinoma was associated with metastatic lesions in the axillary lymph nodes. In the tumors of a lower grade of malignancy, the cells were generally large and ovoid or round, with a generous amount of pale cytoplasm and minor degrees of nuclear hyperchromatism. Larger multinucleated cells showing evidence of more rapid and distorted growth were seen more commonly when the intraductal tumor was solid and when central necrosis was present. The latter, of course, is usually encountered with more rapid growth and in tumors of greater malignancy.

Unfortunately, only 1 tissue slide is now available in the single patient with a tumor of grade 4 malignancy, and it shows a grade 4 intraductal carcinoma without stromal invasion. Obviously, one cannot call this a preinvasive carcinoma on the basis of 1 section, but the case was included in this series because we have no definite proof that stromal spread was present within the breast, although such extension is certain in view of the extensive nodal metastasis.

COMMENT

If one includes under the designation "comedocarcinoma" those growths in which 75 per cent of the neoplastic tissue remains confined to the large ducts, the incidence of this pathologic subdivision amounts to about 6 per cent of all cases of mammary carcinoma. Only 36 of the 603 comedocarcinomas in our series were entirely intraductal. Thus, it is obvious that in situ carcinoma is a rarely discovered lesion in the mammary gland.

According to most investigators, 95 per cent of mammary carcinomas take origin from the ducts. It is perhaps surprising that more carcinomas of the breast do not exhibit the comedo picture and that more of these early, or in situ, lesions are not found. Perhaps the answer lies in the fact that the breast, like the stomach, is prone to develop lesions of a high degree of malignancy and that the in situ phase of these lesions is extremely transitory. If this is true, the biologic mystery of Paget's disease of the nipple is deepened, for sometimes intraductal metastatic tumors of many years' duration may be seen in this disease in connection with deep lesions that frequently are clinically impalpable and that, microscopically, are sometimes confined entirely to the larger mammary ducts.

With operations that are less than radical being curative for such lesions as in situ carcinoma of the cervix, a similar conservative approach might appear to be logical for in situ carcinoma of the breast. However, our studies and those of others have emphasized the extreme difficulty of certifying a lack of stromal invasion. Even if one were able to apply the technique of Ozzello and decide, with the use of special stains, the matter of invasion of the basement membrane, one never could be certain of the supposed in situ location of these growths without studying serial sections of all of the removed mammary tissue. For this reason, and because the number of in situ lesions is so small percentagewise, we hesitate to recommend anything short of radical mastectomy for the lesions under discussion. It scarcely needs

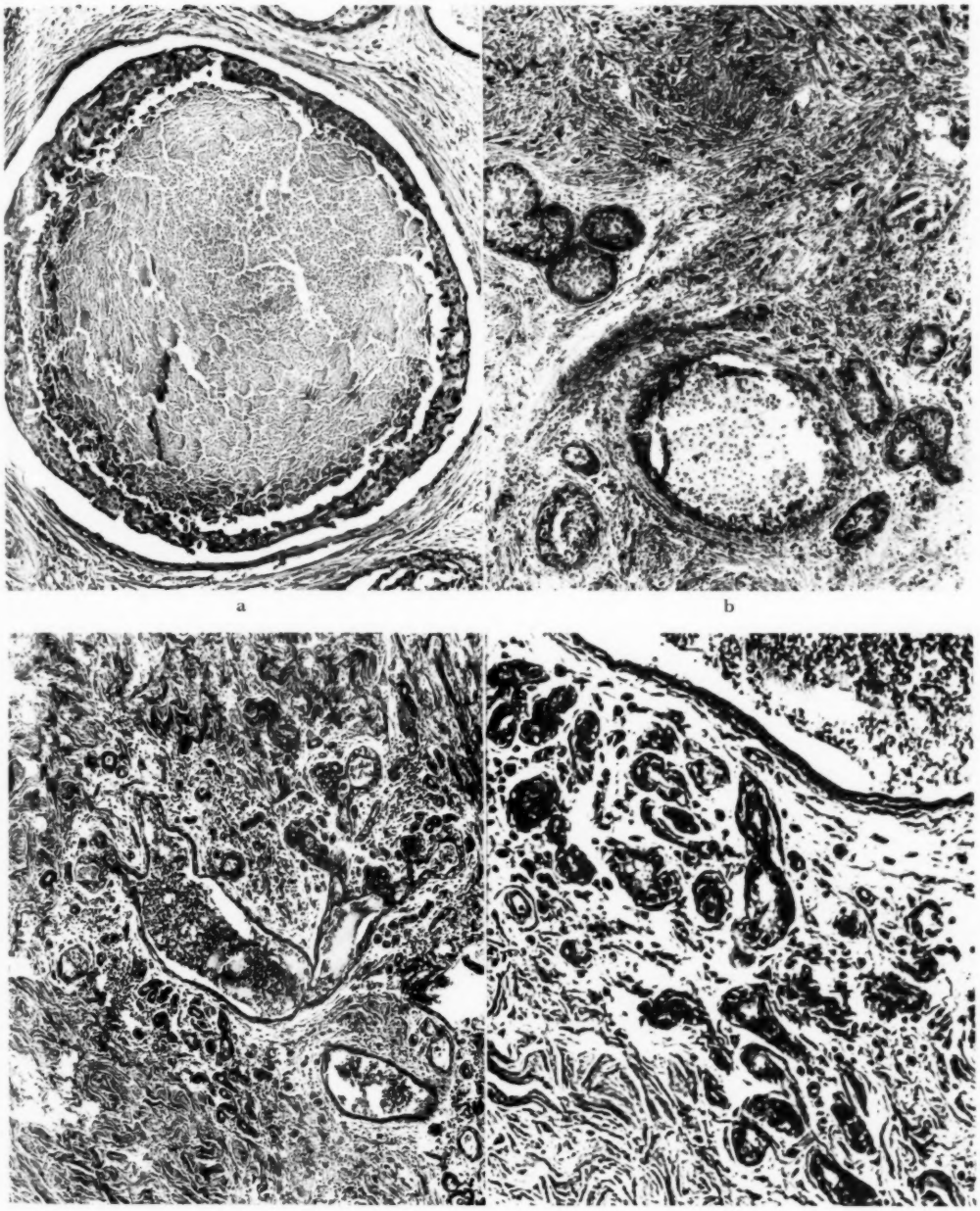


FIG. 3. Intraductal mammary carcinoma. a, Comedocarcinoma with extensive central necrosis. Hematoxylin and eosin, ×80. b, Intraductal and infiltrating carcinoma. Hematoxylin and eosin, ×80. c, Lobular carcinoma in situ. Note distortion of normal lobular architecture. Hematoxylin and eosin, ×80. d, Lobular carcinoma in situ. The obliteration of many acinar lumina by the neoplastic epithelium is well illustrated. Hematoxylin and eosin, ×218.

emphasizing that, after a careful, time-consuming study of 50 tumors believed originally to be in situ with respect to the mammary ducts, no less than 14 of them exhibited foci of obvious stromal invasion. Consequently, we disagree with the concepts of Bloodgood (1), and Foote and Stewart (7, 8) that a policy of conservatism may be pursued when frozen sections do not reveal stromal invasion in "noninvasive" forms of comedocarcinoma.

SUMMARY AND CONCLUSIONS

A study was made at the Mayo Clinic of 36 cases of intraductal carcinoma of the breast in which thorough study confirmed that these lesions were entirely preinvasive. These tumors were obtained from a study of 603 comedocarcinomas of the breast.

Preinvasive intraductal carcinoma of the breast, in its pure form, is an uncommon but distinctive manifestation of mammary carcinoma. This particular variety of breast tumor is not unusual in its age distribution. It does not produce any characteristic symptoms or signs, and the classic clinical signs of malignancy are usually absent. The major gross change is ductal dilatation, with or without visible intraductal plugs of tumor. The affected zone may appear grossly normal.

The accurate identification of this entity requires careful and thorough microscopic study of involved tissue. It is not reasonable to expect the surgical pathologist to state that a given tumor is entirely intraductal on the basis of preliminary review of frozen sections; therefore, the surgeon should not allow the results of this examination to be the final determinant in his decision for or against radical surgical intervention.

The evidence from this study is that carcinoma of the breast does not involve the regional lymph nodes as long as it is still confined to the ducts. Malignant tumors of the breast that are completely intraductal in distribution show a definite tendency to good differentiation.

The life expectancy of patients from whom a preinvasive intraductal carcinoma of the breast has been removed is not altered by the disease.

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EVALUATION OF EXPERIMENTAL ENDARTERECTOMY IN VESSELS OF DIFFERENT CALIBER

DAVID C. SABISTON, JR., M.D., F.A.C.S., GARDNER W. SMITH, M.D., and JAMES L. TALBERT, M.D., Baltimore, Maryland

THE SUCCESSFUL EMPLOYMENT of thromboendarterectomy in the treatment of occlusive arterial lesions secondary to atherosclerosis has led to an interest in the problems associated with the application of this procedure to small vessels. One of the most important problems in current clinical medicine is that associated with coronary atherosclerosis. Recently, attention has been directed toward a direct approach in the surgical removal of localized obstructions in the coronary arteries and several clinical and pathologic studies have been reported. Although experimental investigation of healing after endarterectomy has been extensive, there has been little attempt to relate this process to the size of the vessel involved. The present study has been undertaken to evaluate the results of experimental endarterectomy in systemic vessels of various size including those of a caliber comparable to the size of human coronary arteries.

METHODS

Twenty-eight adult dogs were employed in the study. The animals were anesthetized with ether administered through an endotracheal tube and maintained with a mechanical respirator. In 10 dogs the abdominal aorta was exposed below the renal arteries, and a segment approximately 3 centimeters in length was isolated. Arterial clamps were applied proximally and distally and an arteriotomy was made. An endarterectomy 1 centimeter in length was performed as illustrated in Figure 1. The endarterectomy was performed by careful dissection with small, sharp, curved scissors in a plane through the muscular layer. It was rather striking that this plane was usually found without difficulty, and the intima and a portion of the muscular layer were excised as a single specimen (Fig. 2). In 9 animals, a similar procedure was performed on the femoral artery.

In a second study, 88 per cent phenol was applied to the intimal surface of a 1 centimeter segment of the abdominal aorta and femoral artery. The technique of exposure was essentially the same as in the animals with endarterectomy. Absolute alcohol was immediately applied for neutralization, and this was followed by thorough irrigation with normal saline. All arteriotomies were closed with a continuous suture of No. 5-0 or 6-0 arterial silk. No anticoagulants were employed either during or after the operation. The diameter of the vessel at the operative site was determined after the procedure and in all instances was found to be essentially the same as the initial measurement.

The progressive stages of arterial healing were studied grossly and histologically in 8 additional animals which were sacrificed at periods of 1 to 42 days after operation. All other animals were followed up for 6 to 11 weeks at which time they were sacrificed and arteriograms made. The gross characteristics of the arteries were noted, and the histologic aspects were studied by tissue sections prepared with hematoxylin and eosin, azocarmine, and Verhoeff-van Giesen stains.

From the Department of Surgery, The Johns Hopkins University School of Medicine and Hospital, Baltimore.

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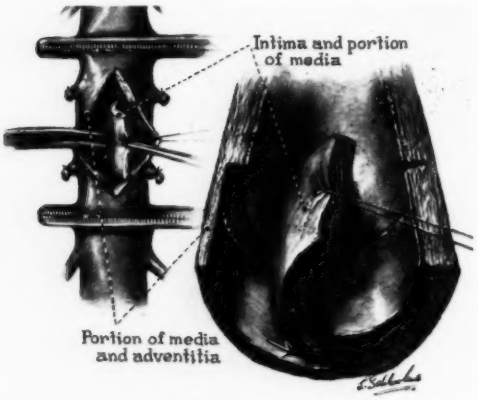


FIG. 1. Illustration of the technique employed in the performance of aortic endarterectomy. The plane of dissection is through the outer portion of the muscular layer of the arterial wall.

RESULTS

Early healing. In the group of animals with endarterectomy which were sacrificed early in the postoperative period, it was found that the endarterectomy defect was quickly obliterated by the deposition of fibrin containing an inflammatory exudate. This fibrin lattice was then invaded by fibroblasts. With the passage of time, this layer became organized with the appearance of an endothelium-like lining. In the animals in which chemical injury of the arterial wall was produced by application of phenol (88 per cent), the muscular layer underwent gradual necrosis within a week, and this area developed into an amorphous hyalinized band. The internal and external elastic lamellae remained intact, although the elastic fibers became slightly fragmented. Fibrin was deposited on the surface and was later invaded by fibroblasts. The hyalinized band which represented the former muscular layer appeared to remain resistant to this cellular infiltration.

Late results. The animals in the second endarterectomy series were followed up for 6 to 11 weeks prior to sacrifice in order to assess the fate of the vessels studied. In all 10 animals with endarterectomy of the abdominal aorta, the aorta was found to be patent. The diameter of the aorta in these animals varied between 6.0 and 9.0 millimeters. In 9 femoral arteries varying in diameter from 3.0 to 4.5 millimeters in which a similar procedure was performed, 8 were patent with 1 instance of total occlusion (Fig. 3a and 4c). The data from the animals with endarterectomy are presented in Table I.

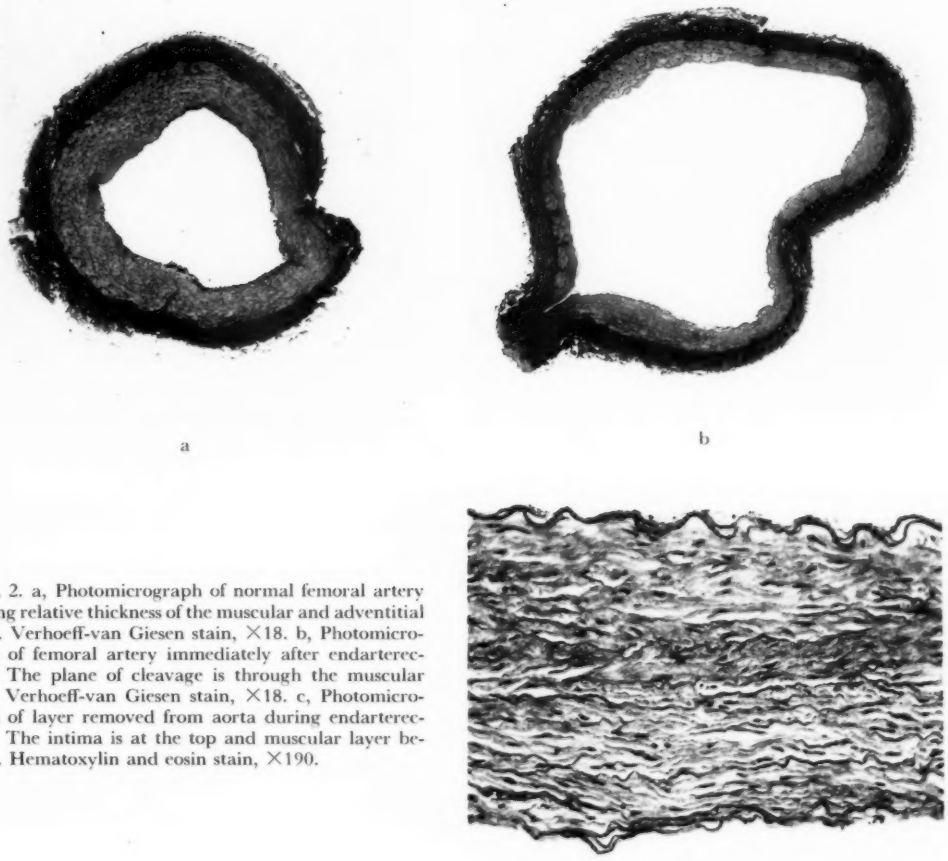
In the series in which phenol was applied, the abdominal aorta remained patent in

TABLE I.—ENDARTERECTOMY

Animal No.	*Diameter, mm.*	*Time, weeks*	*Lumen*	*Microscopic thickening of arterial wall*
		ABDOMINAL AORTA		
3	6.0	6	Patent	Slight
4	6.0	6	Patent	Slight
5	6.0	6	Patent	Slight
9	6.5	6	Patent	Moderate
8	7.0	6	Patent	Slight
10	7.0	6	Patent	Slight
6	7.5	6	Patent	Slight
11	8.0	6	Patent	Moderate
16	9.0	8	Patent	Moderate
23	9.0	11	Patent	Slight
		FEMORAL ARTERY		
9	3.0	6	Occluded	Complete thrombosis
10	3.0	6	Patent	Slight
11	3.0	6	Patent	Moderate
16	3.0	8	Patent	Normal
16	3.0	8	Patent	Moderate
6	4.0	6	Patent	Moderate
8	4.0	6	Patent	Moderate
13	4.0	6	Patent	Moderate
14	4.5	6	Patent	Slight

TABLE II.—PHENOL APPLICATION

Animal No.	*Diameter, mm.*	*Time, weeks*	*Lumen*	*Thickening of arterial wall*
		ABDOMINAL AORTA		
27	6.5	10½	Patent	Slight
25	7.0	10	Patent	Normal
17	7.5	10	Patent	Normal
26	7.5	10	Patent	Moderate
24	8.0	11	Patent	Moderate
28	8.5	8	Patent	Moderate
29	8.5	9	Patent	Slight
21	8.5	11	Patent	Moderate
14	9.0	6	Patent	Slight
		FEMORAL ARTERY		
12	3.5	6	Patent	Slight
13	4.0	6	Patent	Moderate
14	4.0	6	Patent	Slight
17	4.5	10	Patent	Moderate
17	4.5	10	Patent	Slight
26	4.5	10	Patent	Moderate
26	4.5	10	Patent	Slight
21	5.0	11	Patent	Moderate
21	5.0	11	Occluded	Complete thrombosis
23	5.0	11	Patent	Moderate



a b c

FIG. 2. a, Photomicrograph of normal femoral artery showing relative thickness of the muscular and adventitial layers. Verhoeff-van Giesen stain, ×18. b, Photomicrograph of femoral artery immediately after endarterectomy. The plane of cleavage is through the muscular layer. Verhoeff-van Giesen stain, ×18. c, Photomicrograph of layer removed from aorta during endarterectomy. The intima is at the top and muscular layer beneath. Hematoxylin and eosin stain, ×190.

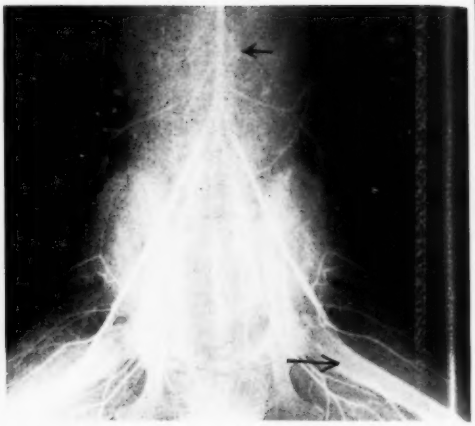
each of the 9 animals studied (Fig. 3c). In the femoral arteries treated with phenol 9 of 10 vessels remained patent with total occlusion in one (Table II).

In the group of animals with endarterectomy and in those with phenol application followed up for prolonged periods (6 to 11 weeks), the histologic sections of the operative sites demonstrated slight to moderate thickening of the arterial wall in some instances, and in several animals this process had progressed to narrowing and in one femoral artery to total occlusion of the lumen. The extent of this change is noted for each vessel in Tables I and II.

DISCUSSION

It has been conclusively demonstrated by a number of workers that endarterectomy is both feasible and successful in the clinical management of occlusion of large vessels such as the aorta and iliac arteries. The femoral, carotid, vertebral, superior mesenteric, and other arteries of intermediate size have also been similarly attacked by DeBakey and associates as well as others, and with good results. Recently the work of Longmire, Cannon, and Kattus has stimulated an increased interest in the possibility of direct surgical removal of atheromas from the coronary arteries. The ultimate success

a



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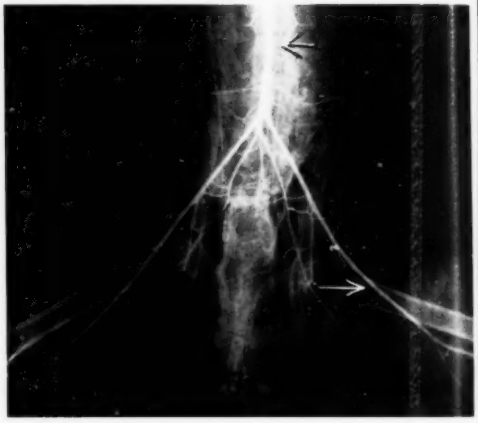

c

FIG. 3. a, Arteriogram 6 weeks after aortic and femoral endarterectomy at site marked by arrows. No significant abnormality can be detected. b, Arteriogram 6 weeks after femoral endarterectomy at site indicated showing complete thrombosis with patency of artery distally. This represented the only thrombosis which occurred in the animals with endarterectomy. The aortic endarterectomy healed with no evidence of narrowing of the lumen visible in the arteriogram. c, Arteriogram 6 weeks after application of phenol to the aorta and femoral artery at sites marked. No significant abnormality can be detected.

of this approach depends upon the ability of the coronary vessels to remain patent after endarterectomy.

The difficulties associated with the application of data obtained from a normal arterial system to the evaluation of one which is diseased are obvious and are immediately recognized. The most important factor in the determination of continued vascular patency after endarterectomy is the degree of patency of the vessels in the peripheral vascular bed. However, it should be noted that there is no evidence to indicate a selective tendency of the coronary arteries to undergo thrombosis after acute injury. In fact, previous experience in our laboratory with the implantation of systemic arteries into various organs has suggested the possibility that the coronary vessels may be selectively protected from vascular occlusion under such circumstances. Implants of arteries into the myocardium were shown to remain patent in more than 90 per cent of specimens whereas similar implants into other organs became totally occluded with the formation of thrombi (6). If these conditions prevail, it would appear that the incidence of continued patency after coronary endarterectomy might be expected to be at least as good as if not better than that obtained in systemic arteries of comparable size.

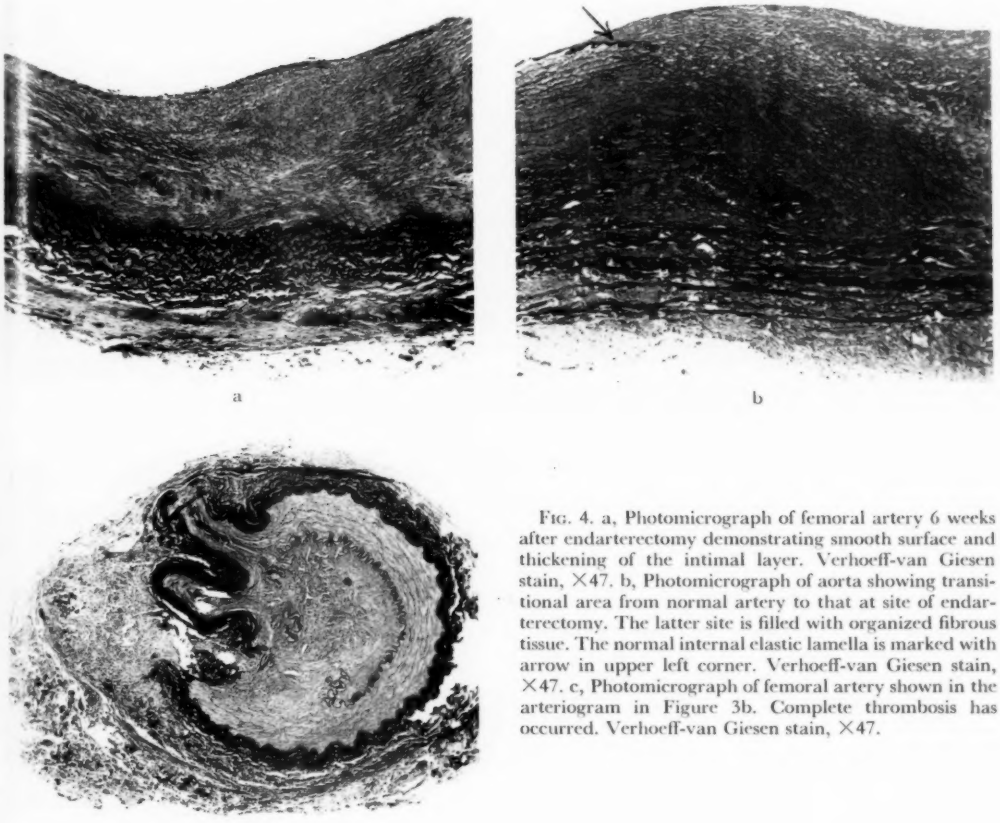

FIG. 4. a, Photomicrograph of femoral artery 6 weeks after endarterectomy demonstrating smooth surface and thickening of the intimal layer. Verhoeff-van Giesen stain, ×47. b, Photomicrograph of aorta showing transitional area from normal artery to that at site of endarterectomy. The latter site is filled with organized fibrous tissue. The normal internal elastic lamella is marked with arrow in upper left corner. Verhoeff-van Giesen stain, ×47. c, Photomicrograph of femoral artery shown in the arteriogram in Figure 3b. Complete thrombosis has occurred. Verhoeff-van Giesen stain, ×47.

In the present study, an attempt has been made to compare the results of experimental endarterectomy in the dog in vessels of large diameter such as the abdominal aorta with smaller vessels such as the femoral arteries. The latter are comparable in size to coronary arteries in the human. Previous investigation on this subject is minimal, and the data available suggest the difficulty of maintaining continued patency in the vessels of small caliber after the performance of an endarterectomy on the iliac arteries of dogs with diameters of 3.0 to 5.0 millimeters.

The data reported here indicate that endarterectomy in vessels the size of the abdominal aorta in the dog is associated with little or no risk of arterial occlusion. In the femoral vessels the incidence of long-term patency was also high (90 per cent). These vessels (with a diameter of 3.0 to 5.0 mm.) are approximately the size of the coronary arteries in man.

In an evaluation of the character of arterial healing following experimental endarterectomy, an attempt has been made to control the factors which might influence this process. The depth of injury has been ascertained by microscopic section, and only those vessels which were comparable in this respect have been included. The peripheral vascular bed has been assumed to be similar in each instance, since only normal stock animals were employed. For the same reason local and systemic factors affecting blood coagulation also have been assumed

to be relatively constant. The fact that the initial stages of arterial healing are completed by 6 weeks has been confirmed. Although certain changes undoubtedly occur after this period, clinical experience with endarterectomy indicates that the majority of the reaction occurs in the first few months.

SUMMARY

In an experimental study, the effects of endarterectomy on the abdominal aorta and femoral artery of the dog were evaluated. The femoral arteries in these animals were comparable in size to the coronary arteries of the human heart and for this reason were selected for comparison. The stages of arterial healing following surgical endarterectomy as well as the changes following chemical endarterectomy are described. The results showed that after aortic endarterectomy the vessels remained patent without significant alteration in the diameter of the lumen. Endarterectomy in the femoral artery was also followed by a high incidence of patency although narrowing was present in some of the vessels. The data support the conclusion that endarterectomy may be performed on arteries of small diameter comparable in size to the coronary arteries of man with expectation of continued patency.

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OBSERVATIONS OF EXPERIMENTAL GRAFTS IN THE INTRATHORACIC VENAE CAVAE

LESTER R. SAUVAGE, M.D., F.A.C.S., and ROBERT E. GROSS, M.D., F.A.C.S.,

Boston, Massachusetts

THE RESULTS OBSERVED during implantation periods of approximately 1 year with three different types of experimental tissue grafts used for replacement of the intrathoracic venae cavae of dogs are reported herein. Although 1 year is too short an observation period to allow for definitive conclusions, the results observed have been so definite that their description at this time has seemed desirable.

EXPERIMENTAL METHOD

Seven dogs weighing an average of 14 kilograms were employed. Each dog was anesthetized with sodium pentobarbital, 30 milligrams per kilogram, administered intravenously. After the induction of anesthesia, moderate hypothermia was induced by immersion of the dogs for a brief period in cold running tap water according to a simple technique previously described (6). All graft implants were performed in an aseptic manner. In each, the right side of the chest was opened through the fifth intercostal space, and the superior and the inferior venae cavae were freed. A 1.5 centimeter segment of the inferior vena cava was excised between Glover arterial clamps after which continuity was restored by means of a 2.5 centimeter length graft. Both anastomoses were performed with running No. 5–0 silk placed as an end-on coaptation stitch. The average period of occlusion of the inferior vena cava was 24 minutes. The mid-descending portion of the thoracic aorta was occluded by a Glover arterial clamp for an average period of 21 minutes during the time that the graft was being placed in the inferior vena cava.

After placement of the inferior vena caval graft, a 1.5 centimeter segment of the superior vena cava was excised between Glover arterial clamps and continuity restored with a 2.5 centimeter length graft of the same type as employed in the inferior vena cava. The azygos vein was left intact. The implantation technique was the same as that employed for placement of the inferior vena caval graft. The average period of superior vena caval occlusion was 28 minutes.

No intravenous fluids or blood transfusions were given to any animal during operation or postoperatively. However, each dog received 600,000 units of penicillin and 0.5 gram of streptomycin intramuscularly the day of operation.

In 2 dogs fresh composite venous autografts made from the right external jugular vein were employed (Fig. 1), in 2 dogs fresh pericardial autografts were employed (Fig. 2), and in 3 dogs ascending aorta homografts preserved 5 days in saline at 4 degrees C. prior to implantation were employed (Fig. 3). These animals were observed carefully after operation, and each was subsequently studied angiographically by the simultaneous injection of 15 cubic centimeters of 90 per cent hypaque into both an external jugular vein and the abdominal inferior vena cava.

RESULTS

The results of these three different types of tissue grafts into the intrathoracic venae

From the Department of Surgery, The Children's Medical Center, and the Harvard Medical School.

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TABLE I.—RESULTS OF TISSUE GRAFTS IN THE INTRATHORACIC VENAE CAVAE OF DOGS

		Angiographic study			*Present*	
Type of graft	*No. of dogs*	*Days after operation*	*S.V.C.*	*I.V.C.*	*Days after operation*	*Status of dog*
Fresh composite venous autografts	1	243	Excellent	Excellent	423	Good condition
	2	235	Excellent	Excellent	414	Good condition
Fresh pericardial autografts	1	240	Occluded	Excellent	—	Died after angiogram
	2	21	Occluded	Excellent	149	Good condition
Preserved ascending aorta homografts (5 days in saline at 4° C.)	1	202	Occluded and calcified	Stenosed and calcified	369	Good condition
	2	221	Severely stenosed and calcified	Stenosed and calcified	362	Good condition
	3	202	Occluded and calcified	Stenosed and calcified	—	Died after angiogram

cavae are shown in Table I. In brief, the fresh composite venous autografts were excellent in both the superior and the inferior venae cavae (Fig. 4). The fresh pericardial autografts were satisfactory in the inferior vena cava but not in the superior vena cava (Figs. 5 and 6). The preserved ascending aorta homografts (5 days in saline at 4 degrees C.) manifested a tendency to occlusion in the superior vena cava and to stenosis in the inferior vena cava (Fig. 7). All of these homografts in both locations became heavily calcified (Fig. 8).

DISCUSSION

The important factors to consider in the selection of a particular type of graft for clinical use in the cardiovascular system are its liability to complications, its ease of technical handling, and its availability. The list of possible complications includes infection, thrombosis (both early and late), embolism, contracture, aneurysm formation, and rupture. All of these complications are considerations of importance for grafts implanted in the arterial system. However, for grafts implanted in the venous system only the complications of infection, thrombosis, embolism, and contracture warrant serious consideration.

The experimental data of Deterling and Bhonslay, Sauvage and Wesolowski, and Bryant, Lazenby, and Howard have demonstrated that arterial homografts in the venous system have an inherent tendency to undergo contracture and thrombosis. The clinical success of Baffes, Riker, DeBoer, and Potts with aortic arch homografts for diverting the inferior vena caval blood into the left atrium in cases of transposition of the great vessels has seemed to be at variance with such data. The successful use of these grafts by Baffes and associates suggested that a segment of the aortic arch in the venous system might have a different fate than would segments of other portions of the arterial system. However, the data of our studies indicate that preserved homografts of the ascending aorta (5 days in saline at 4 degrees C.) have a fate similar to that of homografts of other portions of the arterial system when implanted into the intrathoracic venae cavae of experimental animals. But, it is essential to emphasize that the homografts here reported upon were preserved at 4 degrees C. in a less than ideal medium for 5 days prior to implantation, namely in isotonic saline. Perhaps this preservation method is responsible, at least in part, for the apparent differences between the results of our experimental studies and those of Baffes' clinical series. On the other hand, it is possible that the development of these graft alterations within a few months of implantation could be related to the more rapid life cycle of the dog as compared to that of the human. Longer periods of clinical observation will be necessary to determine

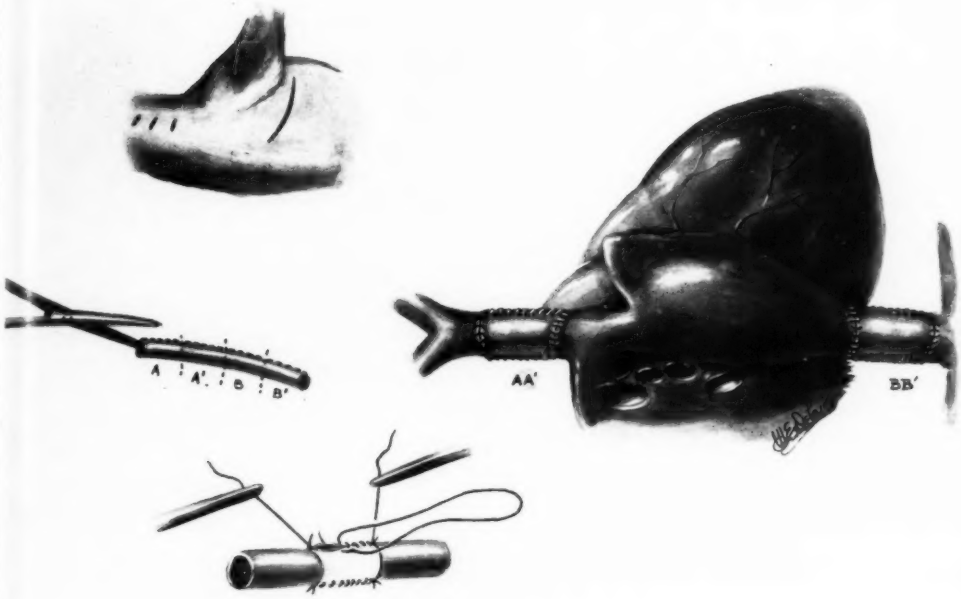

FIG. 1.

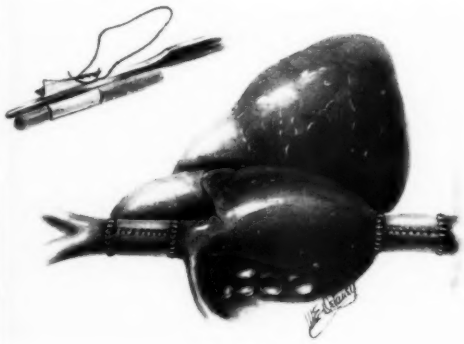

FIG. 2.

FIG. 3.

FIG. 1. Fabrication of double seam composite venous autografts and their implantation into the intrathoracic venae cavae. In 1 dog the grafts were fabricated as shown from 2 opened free segments of the external jugular vein. In the other dog the external jugular vein was transected but once; then, these 2 segments were opened and fashioned into single seam tubes which was accomplished by suturing the upper border of each segment to its lower border.

FIG. 2. Fabrication of single seam pericardial autografts and their implantation into the intrathoracic venae cavae.

FIG. 3. Implantation of ascending aorta homografts, preserved 5 days in saline at 4 degrees C. prior to implantation, into the intrathoracic venae cavae.

FIG. 4.

FIG. 7.

FIG. 4. Angiogram 243 days postoperatively of dog with a fresh double seam composite venous autograft in both the superior and the inferior venae cavae (Fig. 1). Note the smooth appearance of the grafts and the absence of any evidence of collateral venous circulation.

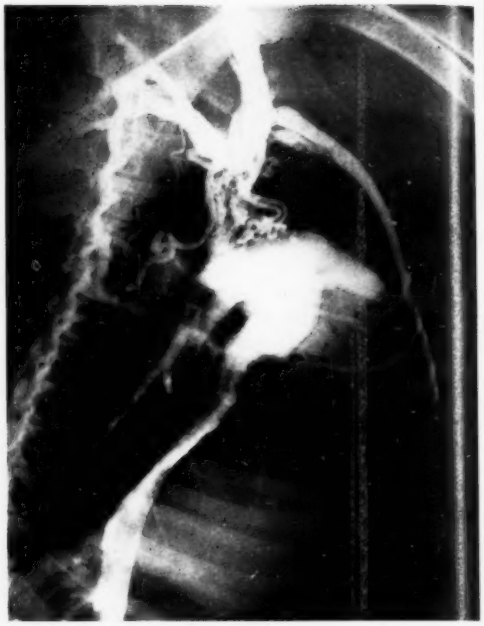

FIG. 5.

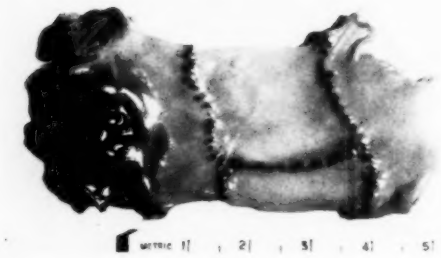

FIG. 6.

FIG. 5. Angiogram 236 days postoperatively of dog with fresh single seam pericardial autograft in both superior and inferior venae cavae (Fig. 2). Note extensive collateral venous circulation about occluded graft in superior vena cava and absence of collateral venous circulation about unobstructed graft in inferior vena cava.

FIG. 6. Open view of the inferior vena caval pericardial autograft (Fig. 5). The dog died a few hours after angiogram procedure. Note excellent healing of both the transverse and longitudinal suture lines, resemblance of the graft to the inferior vena cava, and absence of thrombosis, stricture, or degenerative change in the graft.

FIG. 7. Angiogram 202 days postoperatively of dog with a preserved ascending aorta homograft in both the superior and the inferior venae cavae (Fig. 3). Note the remarkable collateral venous circulation about the occluded graft in the superior vena cava and the stenosis of the graft in the inferior vena cava with the near complete retrograde delineation of the hepatic veins.

a b c

FIG. 8. Fate of preserved ascending aorta homografts (5 days in saline at 4 degrees C.) in the intrathoracic venae cavae at 202 days after implantation. The grafts shown are those of the animal seen in Figure 7. This dog died a few minutes after the angiogram procedure. a, The external view of these grafts is seen. The occluded graft in the superior vena cava is to the left. Note the flattening of the graft in the inferior vena cava and the corrugation of its wall due to contracture. b, The open view of the stenosed graft in the inferior vena cava is seen. Note that its semirigid walls are being forcibly held apart to show the smooth inner surface. c, The plain roentgenogram of this specimen is seen. Note the extensive calcification in both grafts.

if graft contracture will occur similar to that developing in our experimental grafts in animals. Until this essential observation is available, a definite statement relative to the ultimate fate of clinical aortic arch homografts in the venous system cannot be made.

Autogenous pericardium is readily available for use in the intrathoracic venae cavae. Unfortunately, pericardial autografts appear subject to early thrombosis when implanted in the superior vena cava as judged both by our observations and by those of Riberi and Moore. The persistent patency in our study of the 2 pericardial autografts implanted in the inferior vena cava and the loss of patency of both grafts of this type implanted in the superior vena cava are puzzling. We believe that study of the causes of failure of these grafts in the superior vena cava is indicated.

Venous autografts possess the advantages of relative availability and comparative freedom from complications. Defects of important small and medium sized veins may be bridged by means of free grafts taken from nonessential veins elsewhere in the body. Unfortunately, the available autogenous veins are rarely of adequate caliber for use in the venae cavae. The construction of large caliber compilation venous autografts from smaller veins would appear to be a valuable technique in selected instances for grafts of the venae cavae despite the fact that this method is both time-consuming and tedious. Venous autografts are preferred for use in all parts of the venous system. The case of Scannell and Shaw and of Hanlon attest to their clinical value.

Only through the long term study of both experimental and clinical grafts in the venous system will the ultimate fate of these grafts be known. Five of the 7 dogs reported on in this article are being kept for such study. A subsequent report on these animals is planned for after several additional years of observation.

SUMMARY

A series of 14 experimental grafts in the intrathoracic venae cavae of 7 dogs has been presented. Fresh composite venous autografts made from the external jugular vein, fresh pericardial autografts, and ascending aorta homografts preserved in saline at 4 degrees C. for 5 days prior to implantation were studied in 2, 2, and 3 dogs respectively. In each dog, 2 grafts of the same type were employed, one to bridge a defect of the inferior vena cava and the other to bridge a comparable defect of the superior vena cava. From observation of these grafts during implantation periods of approximately 1 year we can say that: (1) fresh composite venous autografts function perfectly in both the

superior and the inferior venae cavae; (2) fresh pericardial autografts function well in the inferior vena cava but undergo early thrombotic occlusion in the superior vena cava, and; (3) preserved ascending aorta homografts (5 days in saline at 4 degrees C.) undergo calcification and stenosis (progressive) in both the superior and the inferior venae cavae with a liability to early occlusion in the superior vena cava. Longer implantation periods are necessary before the ultimate fates of these different types of tissue grafts can be ascertained with certainty. Five of the 7 animals reported upon in this article are being kept for such a study.

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THE MANAGEMENT AND REPAIR OF LESIONS OF THE URETER WITH FISTULA

SIDNEY R. WEINBERG, M.D., F.A.C.S., FRANK C. HAMM, M.D., F.A.C.S., and BENJAMIN BERMAN, M.D., Brooklyn, New York

Ureterovaginal or ureterocutaneous fistula usually follows trauma incidental to pelvic surgery, especially radical hysterectomy or abdominoperineal resection of the rectum. Two important factors demand immediate attention: The first is preservation of the involved kidney, for constriction of the ureter at the site of fistula frequently develops, causing proximal ureteral dilation with hydronephrosis. The ureteral stricture results from two causes, surgical trauma and fibrosis secondary to extravasation of urine into the periureteral tissues. At the beginning, dilation of the excretory passages is reversible, but, if allowed to continue, atrophy of the kidney with complete irreparable loss of function results. The second consideration is relief of external urinary drainage.

DIAGNOSIS

Involvement of a single ureter frequently is overlooked in the immediate postoperative period. Diminution of urinary output and loss of renal function do not occur as the uninvolved kidney maintains normal homeostasis. The symptoms related directly to obstruction of the ureter or extravasation of urine into the periureteral tissues are elevation of temperature, unusual abdominal distention, persistent ileus, and pain over the kidney or in the flank. These symptoms and signs may not be striking and are often overlooked in the immediate postoperative period, being mistaken for disturbances due to the previous extensive surgical procedure.

From the State University of New York, Downstate Medical Center, Department of Surgery, Division of Urology, and the Departments of Urology of Kings County Hospital Center and The Brooklyn Hospital, Brooklyn, New York.

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If the diagnosis of injury to a ureter is to be made, it is important to bear these symptoms and signs in mind, for external drainage of urine from vagina or skin did not appear in our patients until the fifth to the eighteenth postoperative day, and in one patient the urinary discharge did not begin until 4 weeks after operation. From the information available in these case histories, no single factor can be implicated as to the prime cause of the fistula so that clamping, ligating, or stripping of the ureter may have been responsible. Thus, the rate of development of fistula and the appearance of external urinary drainage varies with each patient.

When both ureters are involved by trauma, clinical recognition is made without difficulty as oliguria and anuria result. All the symptoms and signs related to rapid loss of kidney function follow. This is an urgent situation requiring immediate attention. Cystoscopy with an attempt to drain the kidneys by ureteral catheters is indicated. If that is not possible surgical treatment—nephrostomy, deligation of ureters, or a combination of procedures—must be done. The choice depends in the main on the condition of the patient so that a uniform course cannot be recommended.

MANAGEMENT

Once the diagnosis is suspected, excretory urography and then cystoscopy with an attempt at retrograde delineation of the ureters should be performed. Excretory urography demonstrates the condition of the involved kidney, and dilation of the ureter implicates any possible injury even before abnormal urinary drainage begins. At

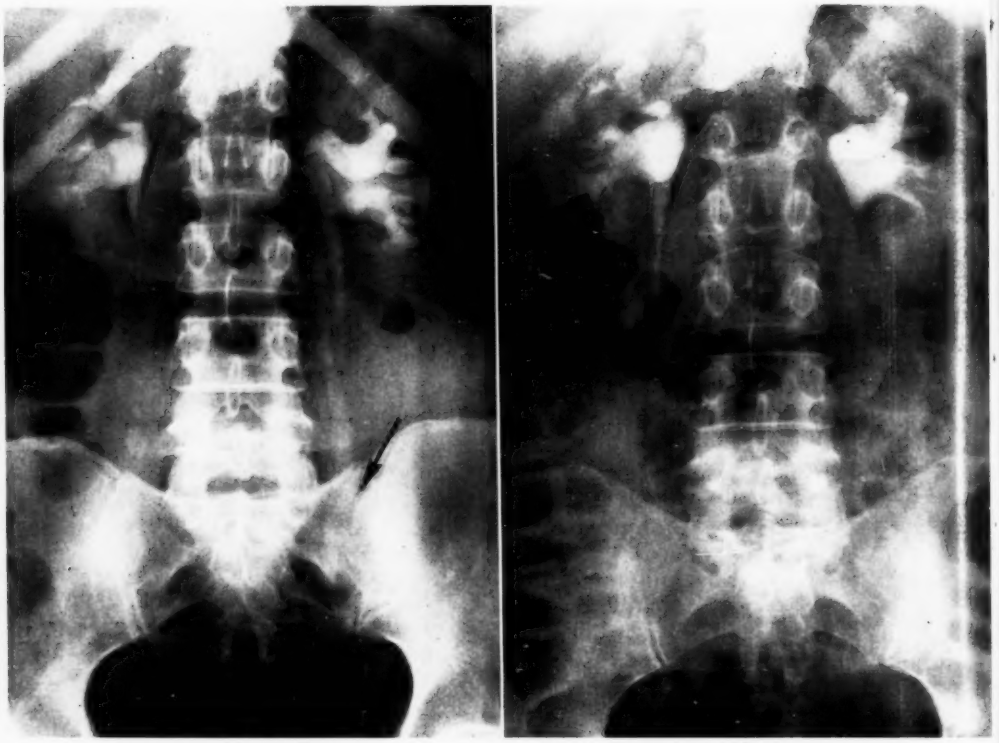

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FIG. 1. Patient H. B. Healing of ureterovaginal fistula without surgery. a, Excretory urogram of 10 October 1950 showing dilatation of ureter and pelvis of left kidney (arrow); ureterovaginal fistula present. b, Excretory urogram taken 7 years later, 23 January 1957, showing normal renal function and structure; ureterovaginal fistula closed spontaneously 10 weeks after appearance.

cystoscopy, differential diagnosis from vesical fistula can be established. Also, it can be ascertained whether obstruction of the ureter is complete. This is most important, for when incomplete obstruction is present, successful healing of the ureter without stricture may result. But when complete obstruction is encountered, hydronephrosis is the outcome without corrective surgery.

As an example of successful nonoperative management of a patient with ureterovaginal fistula and proper healing, in a 42 year old female, urinary discharge developed from the vagina 4 weeks after supracervical hysterectomy. Only once at cystoscopy could a catheter be passed beyond the obstruction in the left ureter. Pyelograms taken at the time of initial cystoscopy showed left ureterectasis and pyelectasis. Ten weeks after operation urinary drainage diminished and then ceased. Excretory urography indicated normal function 7 years after the initial cystoscopy in spite of a bayonet-shaped ureter in the area of the previous injury (Fig. 1).

On the other hand, when obstruction of the ureter is complete, proximal dilation of the ureter and kidney from pressure of urine causes renal atrophy with complete loss of function unless reparative surgery is done. This may account for the spontaneous healing or "cures" that have been noted following ureteral fistula. Liu and Meigs, Spring, and Kulnitz, after examining the kidneys of

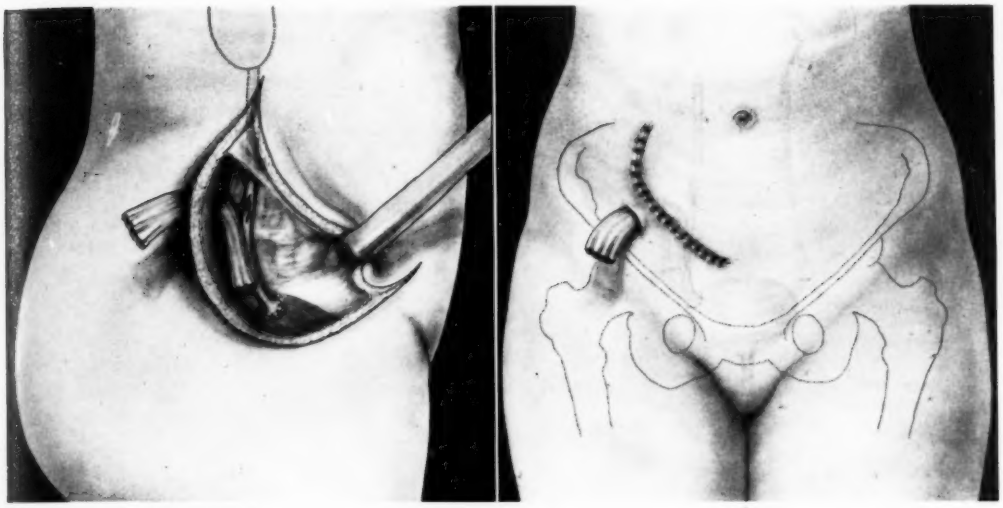

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FIG. 2.

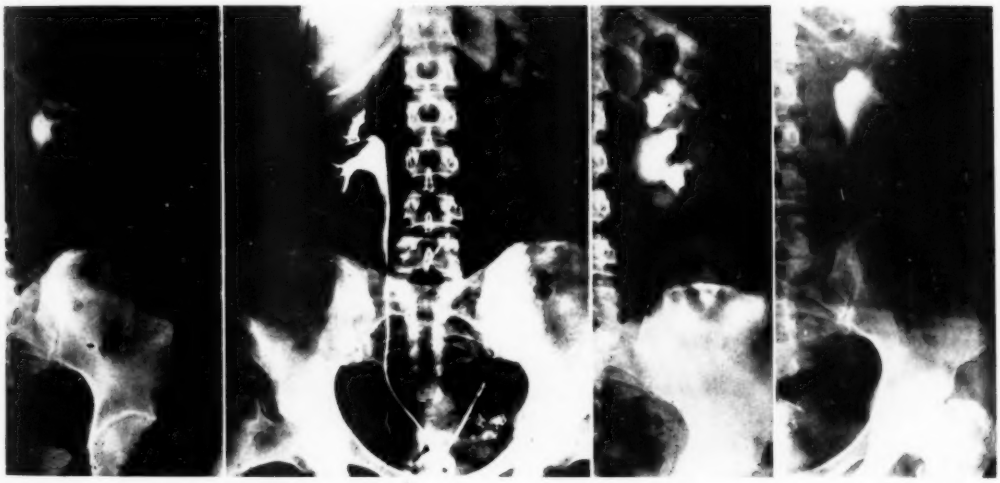

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FIG. 3.

FIG. 2. Method of extraperitoneal ureteroneocystostomy using proximal linear ureterotomy for diversion of urine. a, Side view. b, Incision closed.

FIG. 3. Patient A. P. Demonstration of left ureterovaginal fistula with complete obstruction. Improvement after ureteroneocystostomy noted 4½ years later. a, Preoperative normal left kidney and ureter. b, Complete obstruction to left ureteral catheter. c, Excretory urogram showing marked left calycectasis. d, Excretory urogram made 4 years after ureteroneocystostomy. Note normal renal and ureteral structure and function.

patients with ureter fistulas which closed spontaneously, have reported on this phenomenon. In each instance but 1 of the 17 reported cases, urography demonstrated that the involved kidneys had degenerated. Also, in 2 patients, urinary drainage from a ureter stopped "spontaneously"; the kidneys had no demonstrable function.

FIG. 4.

FIG. 4. Patient L. M. Excretory urograms demonstrating progressive dilatation and destruction of right kidney during course of ureterovaginal fistula, and subsequent recovery. a, Preoperative excretory urogram—normal renal and ureteral function and structure. b, Excretory urogram after radical hysterectomy. Note abrupt block to urine flow at arrow. c, Two months later, dilatation of calyces is advanced. d, Four months after hysterectomy, function of kidney has deteriorated.

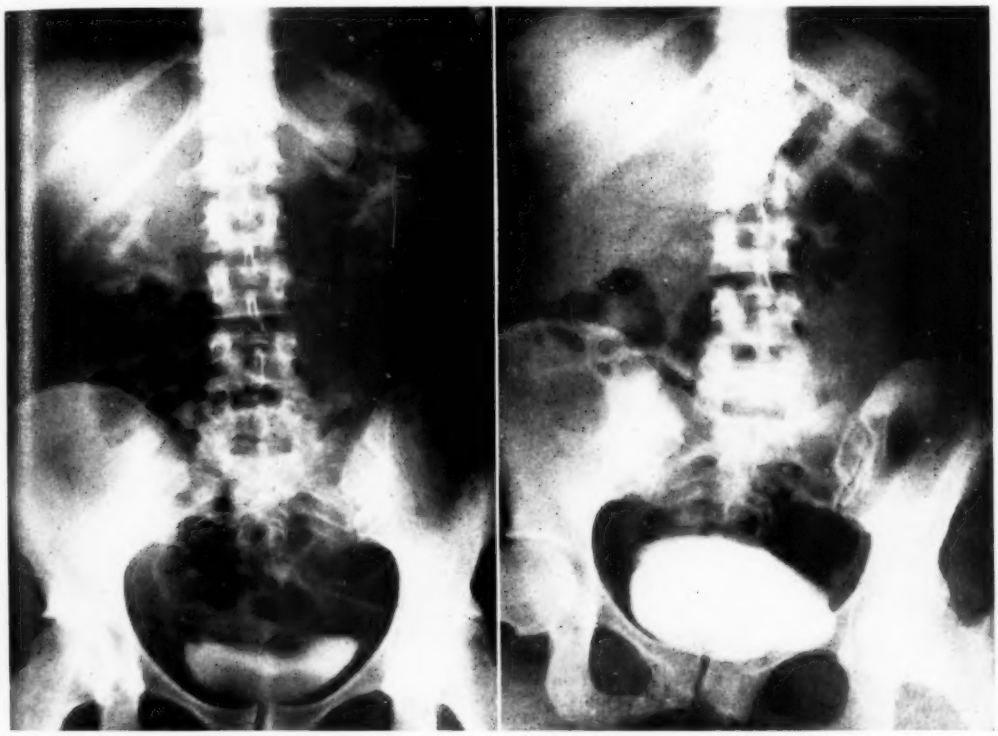
The formation of ureteral stricture at the site of ureterovaginal fistula is comparable to strictures of the ureter formed at the site of experimental defects made in the wall of the ureter in the presence of improper drainage. It has been demonstrated experimentally that the ureter is capable of regeneration in all its coats after the creation of an artificial defect, but only when adequate drainage of urine is provided. In those instances when the drain was removed by the animal before complete regeneration of the defect had taken place, stricture formed at the site of defect. This situation compares with that of a ureter with fistula when urine extravasates into the extraperitoneal tissues.

In summary then, operative treatment for ureteral fistula is indicated when the ureter is obstructed, when there is evidence of toxicity due to pyelonephritis, and when excretory urography demonstrates progressive deterioration of the involved kidney.

SURGICAL REPAIR

Surgical correction of a fistula of the ureter has consisted of: (1) nephrectomy, (2) tying the ureter in the hope that the involved kidney would cease functioning, or (3) reconstructive surgery to eliminate the fistula and re-establish continuity of ureter with the bladder.

Nephrectomy is recommended for those individuals with incurable disease or if the



e f

FIG. 4.

FIG. 4. e, Review excretory urogram taken 15 months after ureteroneocystostomy. Note satisfactory function and disappearance of dilatation noted in preoperative films. f, Retrograde cystogram. Note absence of reflux into right anastomosed ureter.

kidney has been damaged so severely as to preclude return to proper function.

Tying the ureter in the hope that the involved kidney will atrophy silently can lead to serious trouble and is not recommended. Hawkins, Benson and Hinman, and Hamm, Weinberg, and Waterhouse (3) have expressed similar beliefs. In a patient in whom this procedure was carried out for relief of ureterovaginal fistula, severe pyelonephritis was followed by sepsis. The patient died on the fifteenth postoperative day.

Reconstructive surgery is the preferable treatment and is performed by one of two methods: ureteroneocystostomy or direct anastomosis of the stump of proximal segment of the disrupted ureter to the bladder, and end-to-end anastomosis of ureter with excision of the segment involved in the fistula. Although we have advocated anastomosis in instances in which the ureter has been transected and have described a method of repair that has given good results (3), we have not been able to use this procedure for repair of ureteral fistula. In our patients with ureteral fistula, the lower segment of ureter has been involved in dense scar so that the distal ureter was destroyed, making end-to-end anastomosis impossible. The method of choice in this group has been ureteroneocystostomy with the modifications to be described. The modifications are either the construction of an elongated vertical bladder tube flap or the preparation of an isolated segment of small bowel to act as a substitute ureter. These conduits are

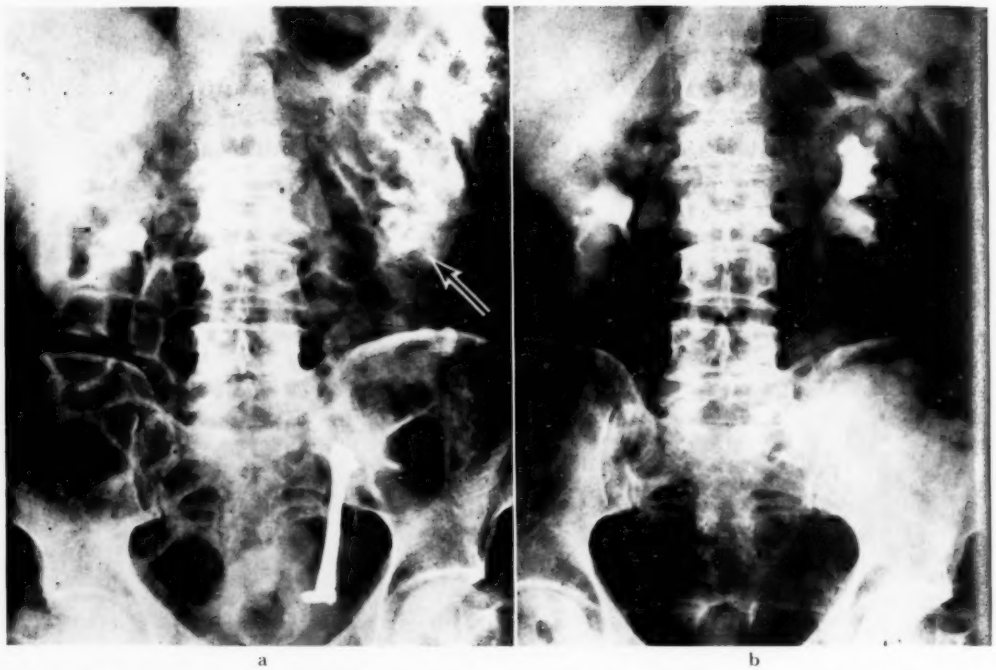


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FIG. 5. Patient P. R. Dilatation and calycectasis of left kidney. a, Excretory urography after abdominoperineal resection of rectum. Note dilatation and calycectasis of left kidney (at arrow) with left ureteroperineal fistula. b, Excretory urogram demonstrating improvement in renal function and structure after repair of urinary fistula.

necessary to bridge the gap between a short proximal ureter segment and bladder. In the past, good results have not been consistent after these plastic surgical procedures. The fact that repair of ureterovaginal fistula has been attempted by many techniques shows that none has been successful universally. The principal difficulties have been inability to identify the ureter in the mass of scar that surrounds the ureterovaginal fistula, difficulty in proper mobilization of the ureter resulting in undue tension, and the ill effects of stagnant urine about the anastomotic site. The unsuccessful repairs have been trailed by infection caused by stasis of urine proximal to stricture. Secondary nephrectomy then becomes inevitable.

To insure a successful result it is essential that the principles of plastic surgery be followed, specifically: (1) The parts to be anastomosed must have adequate blood supply. (2) The anastomosis must not be under tension. (3) Adequate drainage is provided. (4) A factor that pertains specifically to plastic surgery of the urinary tract, stagnant urine, must not be allowed to accumulate about an anastomotic site as infection and stricture of the anastomosis can result.

The four cardinal principles were applied as follows:

1. As the blood supply of the ureter is mainly in its fibrous sheath, the ureter was not unduly traumatized by stripping, excessive handling, or the use of too many sutures, so that sufficient blood was allowed to be present at the ureter end. The bladder is very vascular, presenting adequate blood supply at its end of the anastomosis.

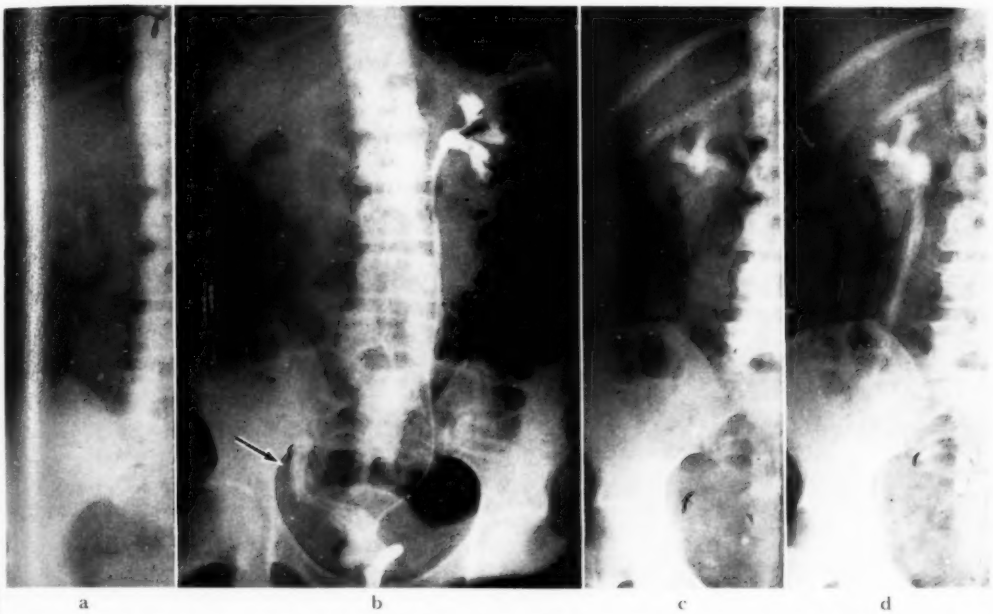

FIG. 6. Patient M. P. Repair of ureterovaginal fistula by ureteroneocystostomy after formation of bladder tube flap. a, Normal preoperative right upper urinary tract. b, Retrograde catheterization of right ureter showing complete obstruction of ureter after right ureterovaginal fistula (arrow). c, Improvement in renal function after ureteroneocystostomy into bladder tube flap 6 weeks after operation. d, Oblique view of same.

2. As the degree of tension at the anastomotic site varies mainly with the length of ureter proximal to the fistula, a ureter of questionable length should be mobilized to diminish the degree of tension. In our patients, the involved ureter was mobilized from the junction of its middle and upper thirds to the area of fistula, which was usually just below the bifurcation of the iliac vessels. It was then brought directly to the bladder in a straight line eliminating the lateral course that an unmobilized ureter takes over the side wall of the pelvis. Also, when the ureter was too short to reach the posterior or lateral wall of the bladder, the peritoneum was incised, the ureter sutured to the dome of the bladder, and the peritoneum then closed anterior to the anastomosis, placing it in the retroperitoneum. These expediencies are preferred to making an anastomosis that would be under tension.

3. Drainage of the operative site was no problem as a simple rubber tissue drain from the retroperitoneal area to the skin wound allowed proper egress of tissue fluids and any extravasated urine. It is essential that the drain be left in place for at least 10 to 14 days; this period of time is needed before a firm, watertight anastomosis is formed.

4. Stasis of urine about the anastomosis is eliminated by means of vertical linear ureterotomy above the anastomosis. In our laboratory, by using an electromanometer to record peristalsis, it has been demonstrated that linear ureterotomy proximal to an area of ureteral surgery leaves the ureter quiescent, that is, with infrequent peristaltic contractions of very low amplitude until healing is complete. By this device, urine can be kept away from the anastomotic site for approximately 10 days, a period of rest necessary to allow regression of dilation and edema. After this time, the linear ureter-

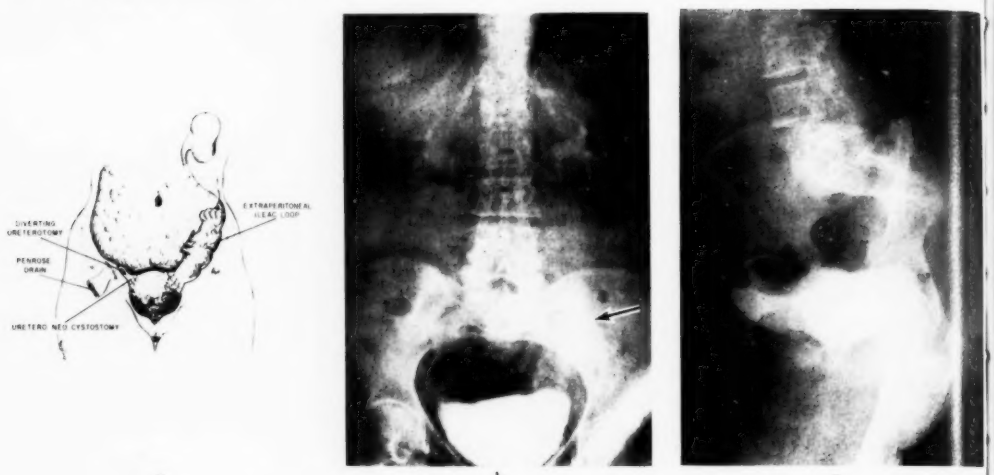

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FIG. 7. a, Diagram of surgical repair of bilateral ureterovaginal fistulas. b, Patient B. N. Excretory urogram made 18 months after simultaneous repair of bilateral ureterovaginal fistula by right ureteroneocystostomy and preparation of left ureter substitute of isolated segment of small intestine (at arrow). Note bilateral satisfactory renal and ureteral function and structure. c, Retrograde cystogram with no reflux into ureters.

otomy has healed with resumption of normal peristalsis of the ureter. Now, urine can be propelled into the bladder through the intact new orifice.

This technique of urine diversion obviates the necessity of intubating the ureter with a catheter. It has been demonstrated that large intubated catheters in the ureter inhibit satisfactory peristalsis and urine flow. Small catheters do not inhibit peristalsis but neither do they divert urine adequately. Also, as catheters are foreign bodies they may introduce infection. Finally, ambulation and care are simpler for a patient without an external drainage tube.

The details of the technique used for ureteroneocystostomy are as follows: The patient is placed supine on the operating table which is rotated laterally away from the side of the body with ureteral fistula. An incision is then made from the pubic tubercle curving cranially and laterally in line with the inguinal canal to a point 5 centimeters above the external iliac crest. The incision is deepened through the oblique muscles of the abdomen in line with their fibers to allow entrance into the retroperitoneal space. At this stage, the peritoneum is retracted toward the midline. The ureter is identified beneath the peritoneal fold above the brim of the pelvis, in an area that was not traumatized by previous surgery. These maneuvers are aided by the lateral tilt of the patient. The ureter is held by a rubber tissue drain and mobilized toward the fistula. Usually, the disrupted ureter breaks free of adhesions a short distance below the bifurcation of the iliac vessels. After necrotic debris is excised from its terminal end, it is approximated to the bladder. The site of the anastomosis can be delineated and held in place with stay sutures put through the bladder wall. A No. 5 French catheter is then passed into the ureter as a temporary aid to facilitate manipulation.

Before anastomosis is begun, a linear ureterotomy for diversion of urine is made by incising the ureter for 2 to 3 centimeters in a longitudinal direction as far above the anastomotic site as possible, usually about 8 centimeters. The bladder is then incised between its stay sutures, also in a longitu-

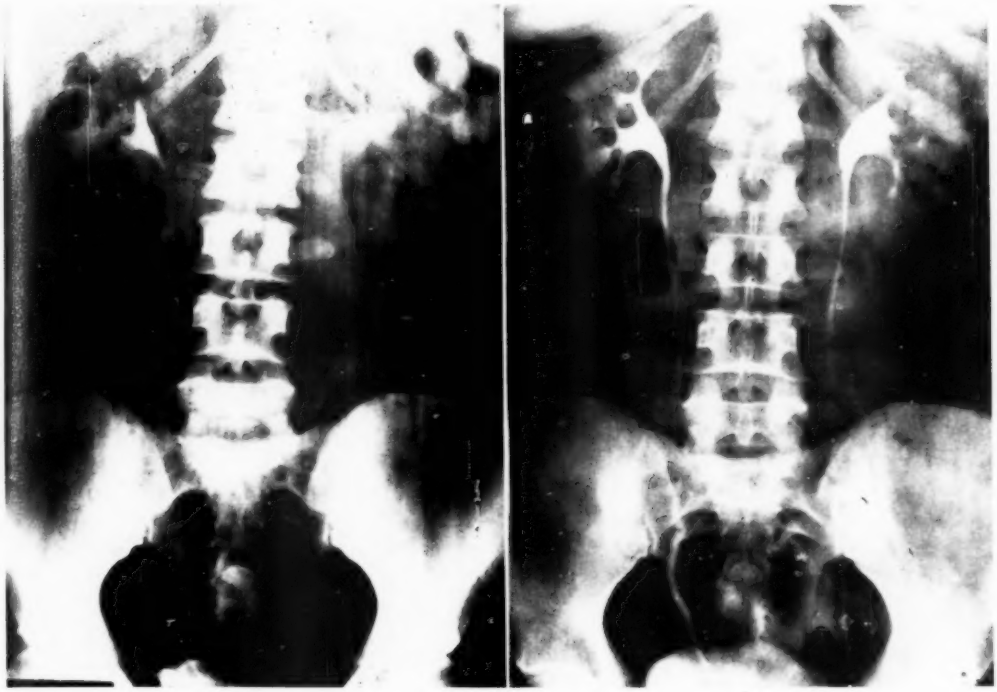

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FIG. 8. a, Patient M. P. Dilatation of left ureter and poor function of left kidney with left ureterovaginal fistula. b, Excretory urogram 6 weeks after ureteroneocystostomy. Note regression of dilatation and improvement of renal function.

dinal direction for 2 centimeters, and a direct mucosa-to-mucosa anastomosis is made by interrupted No. 000 chromic catgut sutures on an atraumatic needle. A few additional interrupted sutures are then placed between the adventitia of the ureter and the outer layer of the bladder to secure the anastomosis. The ureteral catheter is withdrawn before the anastomosis is completed. Finally, a rubber tissue drain is placed alongside the diverting ureterotomy and brought through the muscles and fascia of the abdomen into the center of the skin incision. The bladder is drained by a large indwelling urethral catheter. A No. 26 or No. 28 Malecot catheter can be used in the female patients and a No. 22 or a No. 24 Foley catheter in the males. The wound is then closed in layers (Fig. 2). The patients are allowed to be ambulatory the day after operation. The bladder catheter and the retroperitoneal rubber tissue drain are left in place at least until the tenth postoperative day. By that time an adequate sinus has formed to avoid pooling of urine, if urinary drainage has persisted for an additional period.

RESULTS

In 10 patients with fistula of ureter, treatment was as follows: in 1 patient, ureteral dilatation by means of a catheter beyond the fistula, with a satisfactory result; in 2 patients, no treatment except observation, resulting in renal atrophy; in 1 patient, tying the ureter resulted in death; in 4 patients, ureteroneocystostomy, with satisfactory results; in 1 patient, ureteroneocystostomy with

formation of a bladder flap, with a satisfactory result; and in 1 patient, simultaneous repair of bilateral fistulas, formation of iliac substitute ureter and ureteroneocystostomy, with a satisfactory result.

SUMMARY

Ten patients with fistulas of the ureter have been studied with the following conclusions:

Once the origin of a urinary fistula has been established as coming from a ureter, expectant therapy is recommended only if the ureter is not obstructed, that is, only if a catheter can bypass the fistula and be directed into the renal pelvis and if there is no deterioration of renal function. For the obstructed ureter, prompt repair by operation is necessary for salvage of the involved kidney. The operation used, ureteroneocystostomy, has been performed in 6 patients with good results and with innovations, namely elimination of splints and diversion ureterotomy. In 1 patient, diversion ureterotomy was not used as the ureter demonstrated good peristalsis; a satisfactory result was obtained. In another patient, a bladder tube flap was needed; in yet another, bilateral fistulas were repaired simultaneously by using a substitute ureter composed of an isolated segment of small bowel on one side.

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LUNG BIOPSY

THOMAS W. SHIELDS, M.D., and STANFORD K. SWEANY, M.D., Chicago, Illinois

DIFFUSE PULMONARY DISEASE presents a challenging diagnostic problem. Lesions diffusely scattered throughout the lung may be manifested by debilitating respiratory symptoms—dyspnea, cough, and sputum production—by constitutional findings—fever, weakness, malaise, and weight loss—or may be asymptomatic and discovered only on routine roentgenography. Such lesions may result from the dissemination of fine particulate material into the lungs by inhalation or through the vascular or lymphatic circulations. Diffuse lesions of the lung may also represent pulmonary involvement by a systemic disease or may be a congenital abnormality.

The clinical history, including geographic and industrial exposure, and complete physical examination to detect the general presence of infection, neoplasm, and systemic or cardiovascular disease are essential in establishing a tentative diagnosis. Adequate laboratory study with sputum culture and cytologic evaluation, skin tests, and complement fixation studies may add support to a tentative clinical diagnosis. In most instances, however, tissue confirmation by histologic examination or culture is the only definitive step to a final diagnosis.

Scalene node biopsy is a relatively simple technique and may be utilized on occasion to obtain tissue for diagnosis in such patients. However, in the study of the value of nonpalpable scalene node biopsies, Shields and associates found that in patients with disseminated lung disease—exclusive of sarcoidosis—a positive diagnosis was established in only 20 per cent by the scalene node biopsy. In patients with sarcoid, a positive biopsy was obtained in 80 per cent, though, when only diffuse pulmonary disease was noted without roentgenographic evidence of hilar node enlargement, the biopsy was frequently negative. A more direct method of obtaining tissue for diagnosis in such patients would then seem indicated.

Direct lung biopsy is a simple and a relatively benign procedure. The value of lung biopsy in establishing the diagnosis in diffuse pulmonary disease has been adequately demonstrated by the experience of Andrews and Klassen, Theodose and associates, and Effler and Van Ordstrand. Nonetheless, it is not unusual to have a patient referred for biopsy only after many nonfruitful diagnostic procedures have been carried out. Consequently, a marked lapse of time occurs before the discovery of the diffuse pulmonary disease by roentgenography and the establishment of a definitive diagnosis. The technique utilized by us and the results obtained are described in an effort further to establish the value of the procedure of lung biopsy and to advocate its early employment in such patients. The procedure may be readily used even in patients who are respiratory cripples and who would be unable to tolerate a major thoracotomy as a definitive procedure.

TECHNIQUE

The technique favored by us is essentially that described by Klassen and associates in 1949, except that local anesthesia with positive pressure breathing is preferred to general anesthesia with or without the use of an endotracheal tube.

The area of maximal parenchymal involvement is determined by roentgenographic study and the site of incision is located in the interspace corresponding to the selected area. If the disease is equally disseminated, the right fourth or fifth an-

From the Surgical and Medical Departments of the Northwestern University Medical School, Veterans Administration Research Hospital, and the Chicago Municipal Tuberculosis Sanitarium, Chicago.

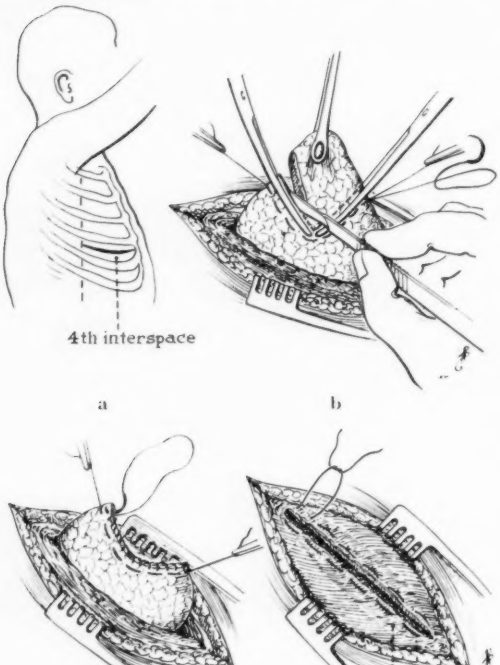

FIG. 1. Technique of lung biopsy. a, Site of elective interspace incision in a patient with bilateral diffuse disease. Patient in supine position. b, After incision is completed through parietal pleura, the site of lung biopsy is grasped with a Duval clamp and Carmalt clamps are placed for excision of the wedge. Continuous sutures are placed under the clamp before excision of the wedge. c, Cut surface of the lung is oversewn with continuous sutures to control any bleeding or air leaks. d, Intercostal incision is closed without pleural drainage. No attempt to close the intercostal muscle is made. Pectoral muscle reapproximated only. Then the subcutaneous and skin are closed in routine manner.

terior interspace is selected as a routine procedure (Fig. 1a).

Adequate preoperative sedation is essential when local anesthesia with positive pressure breathing is to be utilized. A struggling, coughing patient is difficult, if not impossible, to work with. Intravenous administration of fluids should be started and the patient instructed in the use of the anesthetic mask to avoid fear when it is placed over his face during the procedure.

The patient is placed in the supine position and after preparation and draping of the anterior part of the chest wall, the selected intercostal site is infiltrated with 1 per cent xylocaine. An 8 to 10 centimeter incision is then made and carried down through the tissues of the chest wall to the pleura. With opening of the pleural space, oxygen is given under positive pressure by a tight-fitting face mask. The lung is palpated and the selected site of biopsy is grasped with a Duval lung clamp (Fig. 1b). Wedge clamps are placed and running, basting sutures of No. 3-0 black silk are inserted beneath the clamps. The specimen is excised, and the clamps removed. The cut surface is then oversewn with continuous sutures of the same material (Fig. 1c). The area is checked for bleeding or air leaks. If none are found, the lung is dropped back into the pleural space and the incision closed by reapproximation of the pectoralis muscle, subcutaneous tissue, and skin (Fig. 1d). No attempt is made to approximate the divided intercostal muscle in the closure.

Drainage of the pleural space is not carried out if the technique of local anesthesia and positive pressure breathing has been utilized. On the other hand, when general anesthesia has been used because of the patient's apprehension or by design, water seal catheter drainage for 24 to 48 hours has been necessary to evacuate the pleural space completely.

MORBIDITY AND MORTALITY

The complications have been minimal in our experience. Pneumothorax did not occur when the procedure was performed under local anesthesia, though there were several instances when general anesthesia was used. One late case of pneumothorax in a patient with emphysema occurred which promptly responded to intubation. No other major complications have been seen, though subcutaneous emphysema, intercostal hematoma, hemothorax, atelectasis, pleuritis, intercostal neuralgia, and local lung reactions have been noted in the reported series.

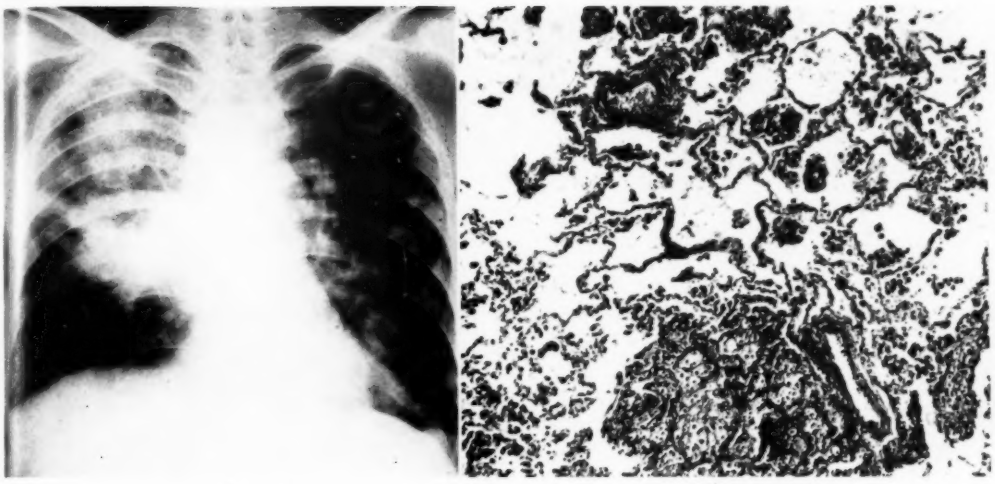

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FIG. 2. Case 15, R. B. a, Scattered soft infiltrates, confluent in the upper field of right lung. b, Histologic section showing nests of tumor cells. ×70.

No death has occurred in the present series, though deaths have been reported by Andrews and Klassen and others; however, in the latter series the procedure per se could only slightly, if at all, be implicated as a precipitating factor.

RESULTS

Thirty-six lung biopsies have been carried out at the Veterans Administration Research Hospital, the Chicago Municipal Tuberculosis Sanitarium, and in our private practice. Not all have been performed by the technique described, though it is now our preferred method of approach. The results of these 36 biopsies in 35 patients were as follows: A definitive diagnosis was made in 31 of the 35 patients, 89 per cent. The results were nondiagnostic in 3 patients, 9 per cent, and 1 diagnosis was proved wrong by subsequent study (Case 7). Follow-up study eventually established a diagnosis of sarcoidosis in this patient. In the 31 patients in whom the biopsy was definitive, the preoperative diagnosis was confirmed in 17, 55 per cent, and determined to be erroneous by the final tissue diagnosis in 14 patients, 45 per cent. The prominent pulmonary symptoms, preoperative diagnosis, and histologic diagnosis are listed in Table I.

Brief summaries of 5 patients are presented as examples of the value of this procedure.

CASE 15. R. B., a 38 year old warehouse worker from rural Illinois, was referred for evaluation of diffuse nodular lesions seen on a roentgenogram of the chest taken at another hospital. He had complained of a progressive weight loss of 45 pounds and fatigue for 18 months. Two months prior to admission, pain developed in the right lower quadrant which was persistent and increased in severity.

Examination revealed a pale, emaciated, white male. His temperature was 100.2 degrees. Scattered ronchi were heard in the chest. There was tenderness in the right lower quadrant but no masses. Significant laboratory findings were a sedimentation rate of 52 millimeters per hour and a blood urea nitrogen of 104 milligrams per cent. Roentgenogram of the chest revealed (Fig. 2a) numerous nodular, fluffy, opacities in both lung fields from 1 to 4 centimeters in size. Intravenous pyelogram showed poor visualization but otherwise normal configurations. Sputum cultures grew normal flora. No fungi or acid fast bacilli were seen. Results of the second strength purified protein derivative (P.P.D.) test were negative, and the histoplasmin was 2+. A tentative diagnosis of systemic histoplasmosis or metastatic carcinoma was entertained. Lung biopsy revealed numerous small nodules, and histologic sections showed these nodules to be composed of tumor cells suggesting metastatic renal car-

TABLE I.—SUMMARY OF CASES

No. *Age, yrs.* *Case*	*Symptoms*	*Clinical diagnosis*	*Pathologic interpretations*	*Clinical diagnosis confirmed*
1[1] 60 A.W.	Cough, dysphagia	Lipoid pneumonia	Lipoid pneumonia	Yes
2 56 L.W.	Cough, exertional dyspnea	Chronic pneumonitis	Congenital cystic disease	No
3 27 W.H.	Fatigue, exertional dyspnea	Sarcoidosis	Sarcoid	Yes
4 64 B.W.	Exertional dyspnea, productive cough	Bronchiolar cell carcinoma	Bronchiolar carcinoma	Yes
5 68 T.K.	Cough	Alveolar cell carcinoma	Metastatic pancreatic carcinoma	No
6 64 H.M.	Cough	Histoplasmosis	Chronic pulmonary fibrosis with calcification consistent with histoplasmosis	Yes
7 40 R.B.	Exertional dyspnea	Metastatic carcinoma	Undifferentiated ca. of lung	Wrong diagnosis
7a Repeat 7	None	Chronic granulomatous infection	Granulomatous infection of undetermined nature	
8 52 E.M.	Chest pain	Alveolar cell carcinoma	Undifferentiated ca. of lung	No
9 38 E.W.	Exertional dyspnea	Alveolar capillary block	Chronic interstitial fibrosis	Yes
10 45 F.D.	Exertional dyspnea	Alveolar capillary block	Minimal arteriosclerosis	
11 46 R.M.	Productive cough, dyspnea	Pulmonary fibrosis	Chronic interstitial fibrosis	Yes
12 33 R.W.	Nonobtainable	Histoplasmosis	Pulmonary alveolar proteinosis	No
13 47 B.J.	Cough	Sarcoidosis	Small vascular thrombosis	
14 69 F.A.	Cough, dyspnea	Pulmonary fibrosis	Congenital cystic disease	No
15 38 R.B.	Weight loss, fatigue	Metastatic carcinoma	Metastatic ca. from kidney	Yes
16 21 C.S.	Fatigue, weight loss	Sarcoidosis	Eosinophilic granuloma	No
17 64 R.K.	Dyspnea, weight loss	Pulmonary fibrosis	Chronic interstitial fibrosis	Yes
18 31 H.D.	Weakness, weight loss fever, hemoptysis	Miliary tuberculosis	Miliary tuberculosis	Yes

TABLE I.—SUMMARY OF CASES—Continued

No. Case / Age / yrs.	Symptoms	Clinical diagnosis	Pathologic interpretations	Clinical diagnosis confirmed
19 53 G.V.	Exertional dyspnea	Silicosis	Silicosis	Yes
20 48 M.P.	Productive cough	Congenital cystic disease	Bronchitis and bronchiectasis	No
21 38 J.D.	Hemoptysis	Sarcoidosis	Pulmonary congestion	
22 31 M.W.	Cough, dyspnea, weight loss	Sarcoidosis	Sarcoid	Yes
23 35 R.B.	Cough, dyspnea, weight loss	Sarcoidosis	Sarcoid	Yes
24 36 A.Z.	None	Pneumoconiosis	Sarcoid	No
25 31 J.L.	Cough and dyspnea	Sarcoidosis	Sarcoid	Yes
26 42 E.M.	None	Sarcoidosis	Pneumoconiosis	No
27 35 M.D.	Chronic cough	Tuberculosis (suspect)	Sarcoid	No
28 34 M.K.	Cough, weight loss	Tuberculosis (suspect)	Chronic nonspecific pneumonitis	No
29 35 P.K.	Cough, dyspnea	Pneumoconiosis	Microlithiasis	No
30 42 S.P.	Cough, fever, chest pain	Tuberculosis (suspect)	Sarcoid	No
31 57 C.B.	Cough	Pneumoconiosis	Pneumoconiosis (silicosis)	Yes
32 57 A.M.	Cough, weight loss	Tuberculosis (suspect)	Pneumoconiosis (silicosis)	No
33 22 A.M.	Asymptomatic	Metastatic carcinoma	Metastatic carcinoma of thyroid	Yes
34[3] 26 J.B.	Hemoptysis, dyspnea	Pulmonary fibrosis	Hamman-Rich	Yes
35 56 O.M.	Dyspnea, arthritis, skin lesions	Eosinophilic granuloma	Eosinophilic granuloma	Yes

[1] = 1-21 Veterans Administration Research Hospital.
[2] = 22-33 Chicago Municipal Tuberculosis Sanitarium.
[3] = 34-35 Private Hospital.

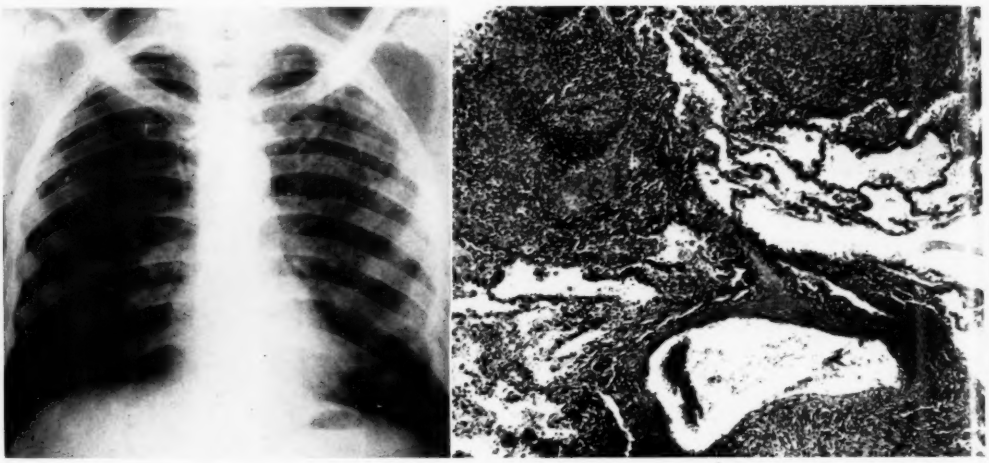

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FIG. 3. Case 18, H. D. a, Fine miliary infiltration. b, Histologic section of lung showing caseous miliary tubercles. ×70.

cinoma (Fig. 2b). Subsequent cytologic study of the urine revealed malignant cells. The patient died 5 weeks after admission. Autopsy revealed carcinoma of the right kidney with extensive metastases to both lungs and the liver.

CASE 18. H. D., a 31 year old colored laborer, entered the hospital with complaints of weakness, fever, weight loss, vomiting, and hemoptysis for 3 to 4 months prior to admission. A roentgenogram of the chest 4 months prior to admission showed "pleural thickening" at the base of the left lung. Examination revealed the patient to have a bizarre mental affect, but he was in no distress. The temperature was 102.6 degrees. There were a few palpable lymph nodes. The remainder of the examination was negative. Blood studies revealed the hemoglobin to be 14.5 grams per cent, the white blood count 7,000, and a sedimentation rate 19 millimeters per hour. Sputum and throat cultures were normal, as were those of the spinal fluid and stools. Results of skin tests, including second strength P.P.D., were negative. Roentgenogram of the chest revealed fine granularity, especially throughout the left lung field (Fig. 3a).

The patient's temperature ranged between 102 and 104 degrees. Despite the negative skin tests and absence of acid-fast organisms, a clinical diagnosis of miliary tuberculosis was considered. In an attempt to confirm this, lung biopsy was performed, and numerous small granulomas were seen to be caseous microscopically (Fig. 3b). Acid-fast organisms were demonstrated histologically, and culture of the tissue was positive for acid-fast bacilli. Specific chemotherapy was then started. Subsequent liver biopsy revealed multiple granulomas. Urine cultures were positive for acid-fast organisms. Roentgenogram of the chest a month after admission showed an increase in the pulmonary infiltration with very fine nodulation, characteristic of miliary tuberculosis. There was a steady improvement in the patient's condition with weight gain, improved appetite, and return of temperature to normal in 6 weeks. Gastric washings have been persistently negative for acid-fast bacilli. The liver granulomas have shown healing on repeat biopsy, and liver function has returned to normal. After 4 months, the disseminated nodules, shown by roentgenologic examination, have cleared. There are some small persistent densities in the upper part of the left lung. The result of test with intermediate strength P.P.D. is now positive.

CASE 9. E. W., a 38 year old white laborer, was referred to the hospital because of progressive exertional dyspnea of 3 years' duration. The only significant historical and physical finding was clubbing of the fingers, which was first noticed by the patient approximately 8 years previously. The roentgenogram of the chest (Fig. 4a) was negative. The result of test with second strength P.P.D. was positive; other laboratory findings were noncontributory. A marked reduction of pulmonary diffusing capacity was found to be present by the carbon monoxide steady state method (6.6 c.c./min./mm. Hg).

Because of the marked reduction in the diffusing capacity along with a normal chest roentgenographically, lung biopsy was considered as an additional means of investigation of this patient's problem. This biopsy revealed chronic organizing inflammation with cellular and foreign body giant cell reaction (Fig. 4b). Though the etiology per se was not disclosed, the anatomic explanation of the diffusion defect was obtained. The patient was given 10

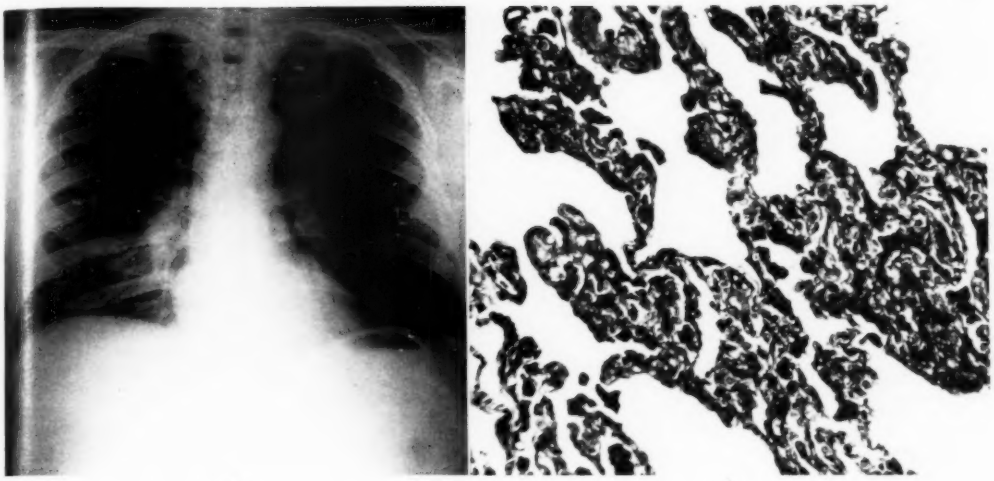

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FIG. 4.

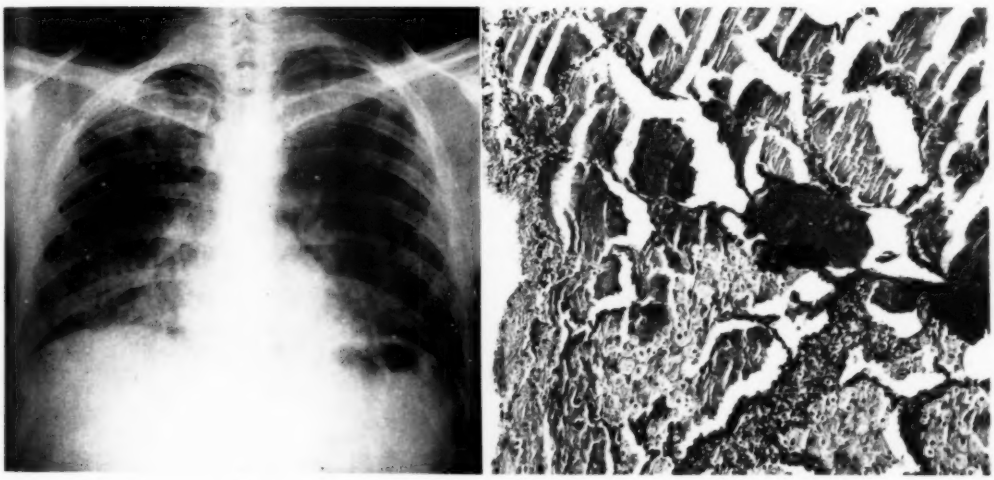

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FIG. 5.

FIG. 4. Case 9, E. W. a, Roentgenogram of chest negative. b, Histologic section of lung showing interstitial fibrosis and cellular proliferation. ×140.

FIG. 5. Case 12, R. W. a, Soft diffuse densities with a tendency to be confluent. b, Histologic section of lung showing homogenous eosinophilic material filling some of the alveoli and distended macrophages filling others. Minimal cellular reaction. ×70.

milligrams of prednisone daily, and no deterioration of his condition has occurred during the past 2½ years.

CASE 12. R. W., a 33 year old white laborer, was transferred from another hospital for evaluation of a chronic pulmonary infiltration by lung biopsy. He had been under treatment for 4 months for a paranoid schizophrenic reaction. Physical examination was negative except for some scattered wheezes throughout the chest. Results of laboratory studies were within normal limits. Routine roentgenogram of the chest revealed numerous small, scattered densities throughout all lung fields (Fig. 5a). The result of the histoplasmin skin test was 2+, all others were negative. All cultures for fungi and acid-fast bacilli were negative.

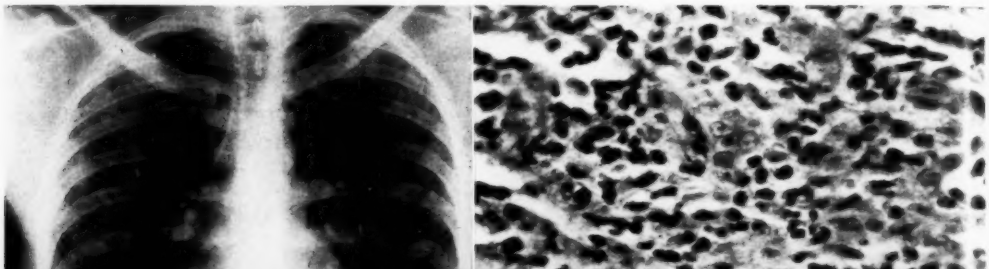

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FIG. 6. Case 16, C. S. a, Moderately soft, symmetrically distributed, nodular infiltrates. b, Histologic section of lung showing high power cellular detail with numerous eosinophils—dark staining with granular cytoplasm. ×380.

Biopsy of the right lung revealed a homogenous, eosinophilic staining material filling the alveoli (Fig. 5b). There was negligible cellular reaction and no disturbance of the pulmonary architecture. The appearance was not unlike thyroid tissue. This was subsequently recognized as being consistent with pulmonary proteinosis. The patient's mental condition, pulmonary symptoms, and roentgenograms of the chest have remained essentially unchanged in the year subsequent to biopsy.

CASE 16. C. S., a 21 year old white gardener from central Illinois, was referred to the hospital because of findings on a pre-employment roentgenogram of the chest 1 month previously that were interpreted as pulmonary sarcoidosis. He had had anorexia, weight loss, fatigue, and exertional dyspnea for 3 months prior to admission. Ten days before admission he experienced severe shortness of breath after mowing the lawn. This was accompanied by sneezing lacrimation and paroxysmal, productive cough. He had experienced a similar episode of respiratory disturbance a year previously after he had started to work in a tree nursery. There were no gross abnormalities on physical examination. The essential laboratory findings were a white blood count of 12,300, sedimentation rate of 26 millimeters, and an albumin-globin ratio of 3.8 to 3.0. Sputum and gastric cultures were negative for acid-fast bacilli and fungi. Roentgenogram of the chest revealed hilar accentuation and numerous moderately soft, nodular densities symmetrically distributed (Fig. 6a). There was calcification at the right hilus. The histoplasmin skin test was 2+. Result of test with second strength P.P.D. was negative. Complement fixation for histoplasmosis was negative. Axillary lymph node biopsy was negative. Lung biopsy was then performed as a definitive diagnostic procedure. In the specimen obtained there were many small nodules, the largest about 6 millimeters in diameter. Microscopic section revealed nearly complete consolidation with numerous eosinophils and various inflammatory cells (Fig. 6b). Neither Histoplasma capsulatum nor acid-fast organisms were identified. Diagnosis was eosinophilic granuloma.

Though no specific therapy was available in either of the last 2 cases, a definitive, though unsuspected, diagnosis was established in each by the lung biopsy.

DISCUSSION

Because of the nature of their pathogenic development, diffuse lesions of the lung offer diagnostic difficulties. The interstitial areas and not the alveolar spaces are involved in the majority of disseminated diseases, with a resultant proliferative tissue reaction. As noted by Rich, the offending foreign material, whether bacterial or tumor, is distributed symmetrically through the vascular and lymphatic systems of the lung into the interstitial areas without extension into the external communicating alveolar spaces. Unless material is excreted and discharged through the bronchial tree, the chance of

identifying the pathologic entity within the lung is slight by conventional means.

The very nature of disseminated disease excludes the possibility of extensive exudation throughout all areas of the lung, since there would not be enough functioning lung tissue to support life. By contrast, localized exudative, pneumonic, or cavitary lung disease offers secretions containing micro-organisms or specific abnormal exfoliated cells. The exception in disseminated malignant conditions is bronchiolar carcinoma. This tumor proliferates within the alveolar spaces and spreads by direct extension from one air space to another. Tumor cells are readily identified in the sputum. Moreover, as shown by Gardner, inhaled substances, unless directly irritative, produce proliferative tissue response. Even when exudation is an accompaniment, the specific irritant or antigen cannot be identified by the cellular exudate produced. Thus, direct biopsy of the involved tissue would appear to be the best method of obtaining a diagnosis.

A definite diagnosis in a patient with diffuse pulmonary disease is important so that specific therapy may be utilized when available. In certain instances, the industrial and medicolegal aspects of the disease—workmen's compensation as a result of industrial dust inhalation—are to be considered. Not least in importance is the assignment of an appropriate prognosis to the patient's disease.

The criterion for a direct and relatively simple and safe diagnostic procedure is met by the pulmonary biopsy. Its use, not as the last diagnostic step but as one of the first procedures, appears warranted. The morbidity and mortality are minimal and the procedure may be carried out even in the respiratory cripple with little risk.

It is conceivable that this technique may be utilized in the study of the complete history of diffuse pulmonary diseases and that a better understanding of the pathologic changes may result. Then histologic, as well as roentgenologic and physiologic, data will be available for study. On occasion, we have utilized this approach in the study of certain patients with only physiologically demonstrable lung defects; i.e., diffusion defects with negative roentgenographic findings. This type may constitute a fruitful field for investigation.

SUMMARY

The value and indications for lung biopsy are presented. A simplified technique of direct lung biopsy under local anesthesia with positive pressure oxygen breathing and no postoperative chest drainage is described. The results of 36 biopsies in 35 patients are presented. A definitive diagnosis was made in 31 of the 35 patients, 89 per cent, from the tissue obtained for the lung biopsy. It was nondiagnostic in 3 patients and wrong in one. In the 31 patients in whom a definitive lung biopsy was obtained, the tentative clinical diagnosis was confirmed in 55 per cent of the patients, whereas, it was found to be unsupported in 45 per cent by final tissue diagnosis.

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BASIC SURGICAL PRINCIPLES OF URETERAL REPAIR

ROBERT G. WEAVER, M.D., F.A.C.S., Salt Lake City, Utah

MUCH BASIC RESEARCH has been done on the ability of the ureter to repair large defects of its wall. These studies have been recorded in several widely scattered journals so that it is difficult for the surgeon to assemble the facts and put them to practical use. Both the laboratory and clinical investigations have been performed primarily by urologic surgeons in their search for more efficient handling of the injured or diseased ureter. From these studies have emerged some basic surgical principles for direct application to the surgery of the ureter. This work also includes basic studies on the physiology of ureteral peristalsis in health and disease, and while there is much remaining to be learned of certain pathologic entities there is, on the other hand, considerable information available regarding the response of the ureter to injury and surgical repair. Since most of these reports are recent, the principles involved have been assembled herein to present in one article not only their proved clinical application but also the laboratory background for them.

Surgical problems involving the ureter were mentioned over one-half century ago, when Albarran described his original attempts to drain the kidney by splinting the ureter. Thirty-five years ago MacArthur described temporary good results in a case of hydronephrosis by splinting the ureter for several days. Since the clinical results had been uniformly far from good, concentrated work on the problem was begun in the past decade.

Although the first concentrated investigation was performed by David M. Davis 16 years ago, much of the subsequent work has been quite recent. In his original study he showed that not only would defects of the ureter heal but also all the components of the ureteral wall would regenerate. Since he performed nephrectomies on experimental animals, several other investigators thought it advisable to repeat these procedures with the kidney intact. The same findings were present in both experiments (Fig. 1).

It is well to have in mind several of the general characteristics of the ureter. First, it is capable of great regenerative powers if the defects are such as to leave a longitudinal strip, even if very small strands remain (Fig. 2). Second, it withstands complete cross sectioning very poorly. Third, a severely injured ureter is capable of regeneration without stricture formation if handled properly, but it withstands overstretching very poorly, and postoperative stricture formation very frequently occurs. Fourth, a thickened and infected ureter is not necessarily permanently incapable of functioning, so that sacrifice of the kidney which it serves is not necessary. Fifth, it can be stripped of much of its blood supply in order to expose it, but strangulation of its ostium by an excessive number of sutures, as during an anastomosis, is tolerated most unfavorably. Finally, the ureter will regenerate a longitudinal defect no matter how long, provided that a strip of tissue containing all components of the wall remains.

IMMOBILIZATION OF THE HEALING URETER

The question has arisen as to whether or not a splint should be used in the ureter. Hamm and Weinberg have reported ureteral regeneration identical to that seen when the defects were not splinted. This observation appeared illogical on the surface, but regeneration occurs repeatedly when defects up to one-half the circum-

From the Departments of Anatomy and Surgery, College of Medicine, University of Utah, Salt Lake City.

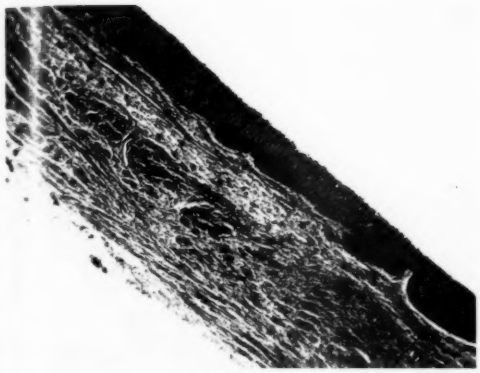

FIG. 1.

FIG. 1. A photomicrograph of the canine ureter after the splinting for 6 weeks of a defect 3 centimeters long involving two-thirds of the ureteral wall. Note the well formed muscularis layer.

FIG. 2. An intravenous urogram taken 4 months after intubated ureterotomy. A defect involving one-half the circumference of the ureteral wall for a distance of 2.5 centimeters was splinted for 5 weeks.

FIG. 2.

ference of the wall have been made for 3.0 centimeters. Two factors are necessary for regeneration to take place under these circumstances, namely, the area must be drained with a soft rubber drain until all urine leakage has stopped, and the ureter must be left within its sheath. This last observation stimulated an anatomic investigation (7) of the surrounding ureteral structures, and it was found that there is a sheath composed of transversalis fascia which is a direct downward extension of Gerota's fascia (Fig. 3). Furthermore, Hinman and Oppenheimer have found that secondary tubular formation occurs if redundant or unattached ureteral tissue is present and thus a useless blind tube is produced.

The clinical problem, therefore, does not resolve itself into an argument as to whether or not to splint the ureter but rather as to whether one or the other method could be used most effectively. For practical purposes, the ureter must be removed from its sheath in cases of severe injury or if operation must be performed upon it. The ureteral sheath not only provides splinting but also prevents periureteral adhesion and allows peristalsis. Therefore, when the ureter remains within the sheath, the intraluminal splint is unnecessary.

The ureteral splint takes a prominent place in the subject of surgery of the ureter as it has been found that a healing ureter requires a considerable degree of immobilization. In the laboratory, no persistent fibrosis or infection has been observed when the splint has been small enough to prevent overstretching of the ureteral wall and if it has been removed within a reasonable length of time, i.e., 4 to 7 weeks postoperatively.

Clinically, the splint is for those cases in which the operative or opened portion of the ureter is removed from its sheath. When the sheath is left intact, as in a ureterolithotomy, no splint is necessary. Also, in those cases in which a plastic procedure is performed on the ureter or renal pelvis, the use of the splint is unnecessary as it is not an adjunct or a substitute for a well placed suture line. This area must be drained, not

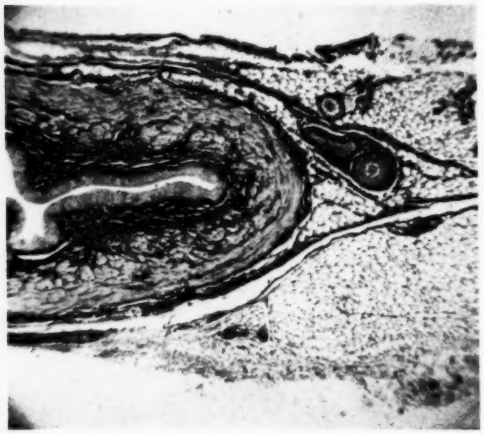

FIG. 3.

FIG. 3. A photomicrograph of a cross section of a canine ureter showing the enclosure of the ureter by transversalis fascia together with its artery and vein.

FIG. 4. A section of ureteral wall in which the splint was left in situ for 3 months. Marked infiltration of all layers with lymphocytes.

FIG. 4.

because the anastomosis must be watertight but because urine must be drained promptly. It is not the presence, but the puddling, of urine around the anastomotic site that produces fibrosis.

SPLINT LEFT IN PLACE A SUFFICIENT LENGTH OF TIME

It was learned from the experimental animal that complete regeneration is seen in 6 weeks when all the component parts of the ureteral wall including smooth muscle are reformed. Objections were raised clinically to splints on the basis that infection or fibrosis would intervene and cause damage to the healing ureter. This problem was then taken to the laboratory where large, constant defects were made in the ureter. The splints were then removed at intervals varying from 10 days to 4 months. Removal of the splint prior to 14 days resulted in a marked periureteral fibrosis with angulation due to insufficient immobilization. This finding is consistent with microscopic observations of the regenerated segments. At 12 weeks, a gross thickening of the entire wall was present with marked infiltration of lymphocytes to all the layers (Fig. 4). The most striking finding was the infiltration between the muscle bundles. The ominous presence of fibroblasts began at this point, but the process was still reversible.

By following the laboratory results it is seen that a splint should be left in situ for more than 2 weeks but there is no point in leaving it more than 6 weeks. Four or 5 weeks will give good clinical results.

TYPES OF SPLINTS AND SPLINTING MATERIALS

Nearly any kind of material, either plastic or rubber can be used; however, Davis reported finding severe fibrosis with total occlusion of both ureters when polyvinyl plastic tubes had been used in a patient who was allergic to this material. When a nephrostomy is performed in the upper part

of a ureter, a soft rubber T or Cattell tube has been used satisfactorily by the author during the past 12 years. Others pass a No. 8 to 10 or 12 plastic catheter through the bladder and urethra which is in turn anchored to an indwelling urethral catheter.

While the material of the splint has importance, great emphasis must be placed upon the size of the catheter. It has been observed that the ureter reacts violently to overstretching of its wall. This produces a marked atonicity with very reduced peristalsis if the process is acute. In a series of dogs, a soft rubber T tube was placed through the regenerating area of the ureter for 4 weeks and then removed. A 90 per cent pyonephrosis resulted with loss of the kidneys from severe fibrosis and an impassable stricture at the area of the tip of the splinting catheter (Fig. 5). When replacement was made by a small but hard plastic tube which did not overstretch the ureteral wall, adequate regeneration with a functioning kidney resulted. Furthermore, in these cases, the diameter of the lumen of the regenerated area was estimated to be 20 per cent larger than the undisturbed portion. This portion, however, reduced to the same dimensions as the remainder of the ureter in several months. The use of oversized splints has been found to produce the same conditions in the clinical patient. A catheter of small diameter should be used, as oversized splints produce fibrosis and stricture formation. It is a normal reaction for the surgeon to wish to use the largest splint possible in order to end with adequate correction of an injured or stenosed area. However, it is better to use a small, firm splint than a large, soft one. A No. 8 or 10 French is usually sufficiently large.

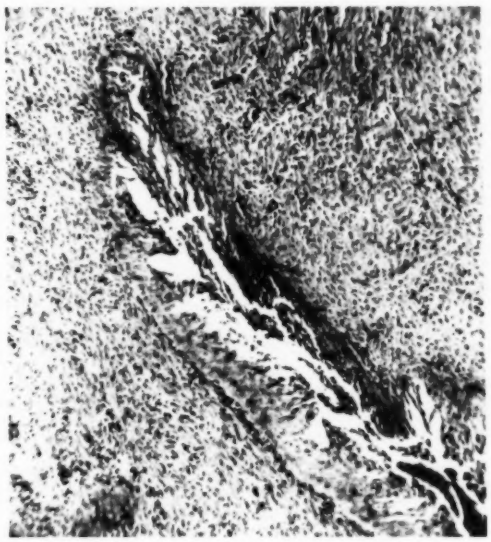

FIG. 5. An impassable stricture with massive fibrous tissue. A photomicrograph of a dog's ureter into which a splint had been introduced stretching the wall.

SITES AND TYPES OF DEFECTS

It has been found that angulation of the healing ureter is best prevented when the adjacent organs, particularly the kidney or the bladder, can be used to aid in the healing by immobilization. The management of ureteral defects, therefore, resolves itself into two factors (1) whether the kidney or the bladder can be utilized for splinting and drainage if a splint is required and (2) whether the ureter is dilated or of normal diameter. The T tube is preferred by some if its use is practical as it remains well in situ and gives drainage either to the bladder or externally.

Operation on the upper half of the ureter will probably give access to the kidney so that this structure may be used for either nephrostomy or pyelostomy drainage. The other arm of the T tube extends for several centimeters below the operative site and into the normal ureteral lumen (Fig. 6).

Defects in the middle one-third of the ureter are usually such that neither the kidney nor the bladder can be used. It is here that the size of the ureter is important. If it is of sufficient size to allow for a small stricture and still retain an adequate lumen, then a small T tube with one arm extending through the abdominal wall is the most expedient and will require the least amount of postoperative care. If, however, the ureter is of normal diameter, a small straight

splint from the renal pelvis above to the bladder below is necessary. A No. 4-0 plain catgut suture through the splint and the ureter below the defect will keep it in place against the peristalsis for a sufficiently long time for regeneration to take place, or until another splint can be replaced from below.

MANAGEMENT OF PERIURETERAL FIBROSIS

The function of the ureter is completely dependent upon its peristalsis to transport urine from the kidney pelvis to the bladder. Periureteral fibrosis may trap the ureter and thus seriously impair its ability to contract. Observations on the peristalsis and ultimate renal function have been made on the ureter of the dog when the regenerated area was encased in perinephric fat. Further work has been done in checking the response of the ureter and perifibrosis to fat and fascia. It was found that the ureter was allowed free movement when encased in adipose tissue. Even though the fat eventually disappeared, fibrosis and angulation of the ureter did not take place. This problem is not present when the ureter remains within its sheath or when severe periureteritis is not present.

The thick-walled, enlarged ureter which may be encountered in surgery returns to normal appearance and function if the obstructing source, and thus the cause of the periureteritis, is removed. In such conditions as these it is well to encase the area of ureteral adherence and constriction in a fatty sheath with loose sutures of No. 5-0 chromic catgut to hold it in place. In cases in which a defect of the wall is present which requires the regeneration of a segment without periureteritis the fat encasement may be helpful, particularly so in those cases in which there is periureteritis with adhesions.

COMPLETE DEFECTS OF THE URETERAL WALL

Up to this point, only those cases in which there has been a partial defect of the ureter, or in which a strip or strand of tissue remains along the length of the defect, have been considered.

When there is a complete interruption of the continuity of the ureteral wall other problems are present, as the ureter withstands complete transection of the wall very poorly. The problem reverts again to peristalsis. The function of the severed ureter has been studied in detail immediately after reanastomosis. Cessation of conduction occurred for as long as 4 months with subsequent reduction in the speed and amplitude of the peristaltic waves and with dilatation of the ureter and renal pelvis above the anastomosis. Later, however, the movements were restored to normal; on the other hand, a greater amount of anastomotic fibrosis produced a longer interval between peristaltic waves at the anastomotic site. It is therefore advisable to refrain from transecting the ureter if at all possible.

It is fairly evident that muscle fibers enter a ureteral defect from pre-existing smooth muscle which lies adjacent to the area, and not from freely circulating elements in the blood stream or metaplasia of fibrous tissue. Hence, when a strip of ureteral wall remains in the gap the regenerating elements must travel only the distance of the ureteral circumference regardless of the length of the defect. On the other hand, a complete defect usually requires a greater distance of travel if the muscle fibers are to bridge this gap. At this point there are minor differences of opinion among investigators as to whether, in a complete disruption of the wall, there is regeneration of smooth muscle or only a mucosal lining to a wall of scar tissue which promptly strictures down. There is also the question as to whether isolated loops of ileum which bridge the gap are a suitable substitute for the ureter.

Others have found that the ureter will fill a gap of up to 2.0 centimeters if proper immobilization of the excised area is carried out. This procedure, however, has not proved very successful.

Clinically, the two main locations of transection are at opposite ends of the ureter, namely, block dissection or transection done in gynecologic operations or avulsion of the

ureter, particularly around the ureteropelvic junction of the kidney. For practical purposes, any complete defect, except for a small distance, requires an ileal loop as the best substitute available to date. However, the optimum method for treatment of the complete defect has not been devised as yet.

SUTURING THE URETER

The techniques of regeneration are used when a defect is in such a position or of sufficient magnitude that the severed ends cannot be approximated and are not intended as a substitute for a well placed suture line in a plastic procedure. Needless to say, very fine sutures of No. 5-0 catgut are used through the muscularis into the mucosa. No. 4-0 silk retention sutures should be used in the serosa or muscularis only. Probably one of the main causes for stenosis at ureter-to-ureter and ureter-to-bowel anastomoses is the use of sutures which are too heavy. One suture of No. 5-0 chromic catgut at each quadrant with 1 loosely placed No. 5-0 silk retention suture placed between these is sufficient in the ureter of average diameter.

A suture which attempts to bridge an area by pulling the ureter is useless as it will cut through the wall and retract. Furthermore, it is unnecessary as such a gap will regenerate adequately if left open. The friable ureter in a pre-existing infection will also regenerate satisfactorily if the infection is drained and treated in the previously described manner.

POSTOPERATIVE CARE OF THE REPAIRED URETER

The postoperative treatment of the regenerating segment resolves itself, in the main, to care of the splint.

It is advisable to maintain sufficient fluid intake; 1,500 to 2,000 milliliters per 24 hours will usually suffice. The anastomotic site should be drained with a soft rubber drain, as it has been found that it is not the presence of urine but the puddling which causes periureteral fibrosis with its accompanying hindrance to ureteral peristalsis.

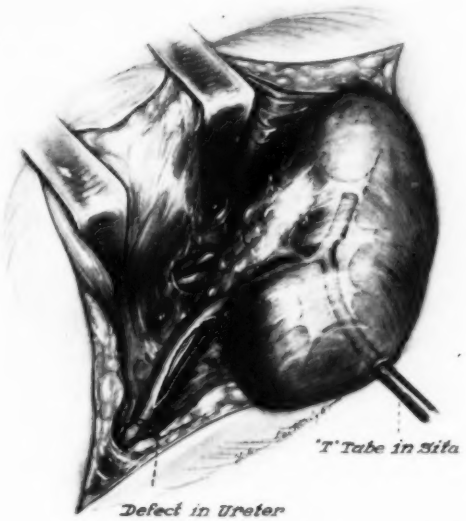

FIG. 6. A schematic drawing showing how the T tube is employed to bridge the ureteral defect. This is only one of several adequate techniques.

Infection is not a problem, being readily controlled by sulfonamide derivatives or broad spectrum antibiotics.

Mineral deposits have been cited as causing blockage of the tube, but these are most frequently phosphate crystals. Their presence in the T tube can be detected early and can be prevented by adequate fluid intake and acid urine which can be maintained by the oral administration of ammonium nitrate, although it is occasionally necessary to irrigate the indwelling catheter with 0.25 per cent acetic acid or Albright's G solution.

SUMMARY

Ten surgical principles governing the diseased or injured ureter have been presented. The laboratory background has been explained and the surgical application of these principles represent a composite of the work done by the investigators and urologists.

The principles involved include the following: (1) Immobilize the healing ureter. (2) Leave the splint in situ long enough for healing to take place. (3) Use the type of

splint which is applicable to the case. (4) Do not substitute a splint for a carefully placed suture line. (5) Use different methods of treating the defects for different sites. (6) Use a fat cushion in the presence of periureteral inflammation. (7) Do not transect the ureter. (8) The complete defect heals poorly. (9) Suture the ureter loosely with fine sutures. (10) Drain the operative site.

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ALTERATIONS IN FAT AND NITROGEN METABOLISM AFTER TOTAL AND SUBTOTAL GASTRECTOMY

WALTER LAWRENCE, JR., M.D., F.A.C.S., PARKER VANAMEE, M.D., ANN S. PETERSON, M.D., GORDON McNEER, M.D., F.A.C.S., SAM LEVIN, Ph.D., and H. T. RANDALL, M.D., F.A.C.S., New York, New York

THE SURGEON who has performed a total gastrectomy is frequently plagued by the patient's severe nutritional difficulties. This situation is particularly distressing in the patient whose cancer has been satisfactorily removed by the operation. This report is presented to record the metabolic observations on a single large series of patients after subtotal and total gastrectomy, and to establish the practical significance of metabolic defects in regard to the nutritional state of these patients. The data presented are those from intake-excretion studies on 25 patients after total gastrectomy and 17 patients after subtotal or partial gastrectomy.

Various objective techniques have been used for physiologic investigations into the etiology, prevention, and management of the symptoms and the absorption problems that follow gastrectomy. Studies of this type have been extensively reviewed by Everson, Kelly and associates, Randall, and many others. There is no question that impaired assimilation of fat and protein does occur in the majority of patients after total gastrectomy. It has been assumed that these defects play a role in the observed changes in nutritional state.

Troublesome symptoms after gastrectomy often form a characteristic clinical picture referred to as the "dumping syndrome," and dietary carbohydrate has been implicated as of great importance in producing these symptoms. This theory prompted us to study the effect of altering carbohydrate intake on fat and nitrogen metabolism. Our curiosity concerning the cause of the absorption abnormalities observed led to an expansion of studies on the effects of dietary adjuvants to include hydrochloric acid. These dietary variations and their effect on the steatorrhea observed have been recently reported by Vanamee and associates and will be briefly reviewed only for comparison with observations on nitrogen metabolism.

From the Department of Surgery, Memorial Center, and the Division of Experimental Surgery and Physiology, the Sloan-Kettering Institute, New York.

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MATERIALS AND METHODS

A total of 103 metabolic balance studies were carried out on 42 patients while hospitalized in a metabolic unit. All food items were carefully prepared in a metabolic diet kitchen. Identical diets were homogenized, and aliquots of these were analyzed in triplicate for fat and nitrogen. Carbohydrate content was calculated from the weight of the ingested food by using the charts of Mattice. After a 3 day adjustment period on an identical diet, 3 day metabolic balance periods were used. Fecal collections were divided by means of carmine markers given at the beginning and end of each period.

Clinical material. Twenty-five patients who had had total gastrectomy were submitted to metabolic study. Six of these cases were previously reported from this laboratory by Schwartz, Bodansky, and Randall, and their data are included in our over-all analysis.[1] In the majority of these 25 patients, after total gastrectomy intestinal continuity was restored by simple esophagojejunostomy

[1]The seventh patient from Schwartz, Bodansky, and Randall (patient, J. K.) has been restudied on several occasions and all relevant data are included.

FIG. 1. Diagrammatic representation of "extended total gastrectomy." Twelve of the 25 total gastrectomies were by this technique.

with end-to-side or Roux-Y technique. One patient had a Longmire jejunal interposition, 3 had an esophagoduodenostomy, and another (H. B.) had a jejunal pouch similar to that described by Limo-Basto. Sixty-three separate studies were carried out in these patients at postoperative intervals varying from 1 month to 8 years, and 4 of these patients were subjected to metabolic study on 2 or more hospital admissions. The underlying disease process was carcinoma of the stomach in all but 6 patients. Two had benign gastric ulcers and 4 had sarcomas. The majority of patients in this series are now living free of clinical evidence of recurrent cancer, and the remainder showed no evidence of recurrence for at least 6 months after the study. Twelve of these patients had en bloc resection of the distal pancreas, spleen, and contiguous ligaments and fascia in addition to total gastric resection. This operation is shown diagrammatically in Figure 1 and has been designated "extended total gastrectomy" by McNeer and associates in the appended tables. These data have been included with data from the 13 patients who underwent simple total gastrectomy since there was no significant difference between the two surgical techniques noted in metabolic tests.

The data from 40 metabolic studies in 17 patients after subtotal gastrectomy are also included in this analysis. The extent of resection in these patients varied from an estimated 70 to 90 per cent of the stomach. Two of these patients underwent resection of the proximal portion of the stomach, and continuity was re-established by esophagogastrostomy. The remaining 15 patients had distal gastrectomy, and all but 2 had a Billroth II type of gastroenterostomy. None of the patients subjected to distal gastrectomy had concomitant vagus section. The indications for surgery in this partial gastrectomy group were carcinoma in 7, lymphosarcoma in 1, gastric ulcer in 3, and duodenal ulcer in 7 patients.

Laboratory analyses. Nitrogen was determined by digestion with selenium-sulfuric acid-hydrogen peroxide and micro-Kjeldahl distillation. Fat was determined by the method of Saxon. Details of the procedures and chemical methods have been described in detail by Schwartz and associates and Vanamee and associates. Regression equations and other statistical evaluations were carried out by standard methods.

RESULTS

In Tables I and II are recorded in detail the data utilized in subsequent calculations along with pertinent clinical data regarding diagnosis, age, operation, weights, and postoperative interval. The 6 cases previously reported from this laboratory by Schwartz and associates are included in Table I and are so identified. The metabolic data on fat absorption previously reported on 14 of the patients after total gastrectomy and 12 of the patients after partial gastrectomy are included in these tables to supplement other data from these same studies. Our findings in regard to fat and nitrogen metabolism will be considered separately.

FAT ABSORPTION

Total gastrectomy. The relationship between the fat intake and fecal fat is charted

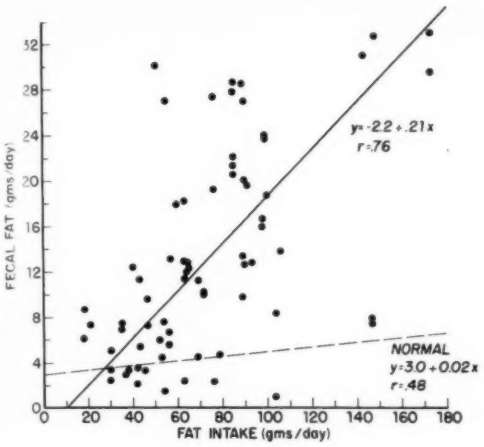

FIG. 2.

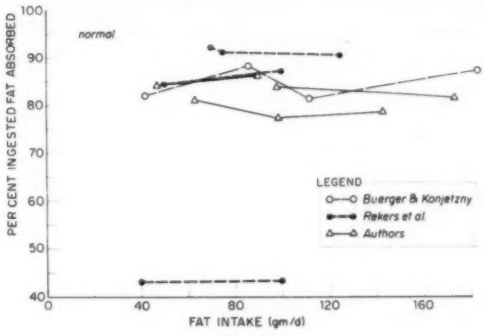

FIG. 3.

FIG. 2. Relationship between fat intake and fecal fat in 25 patients after total gastrectomy (59 studies). Normal data collected by Wollaeger and associates.

FIG. 3. Fat absorption (as per cent of intake) in relation to level of dietary fat in individual patients after total gastrectomy.

in Figure 2. It is apparent that there was extensive variation in fat absorption among these 59 studies on 25 patients. Additional studies were performed during administration of hydrochloric acid supplements which are not included with these data.[2] The range of absorption in this over-all group was 41 to 97 per cent of the dietary intake of fat and the regression equation obtained was $y=-2.2+.21x$ (x = fat intake and y = fecal fat). The correlation coefficient ($r=.76$) was significant ($P<.01$).

From the data of others on normal subjects as well as our own studies on patients without gastrointestinal disease, 92 per cent absorption has been considered as the lower limit of normal fat absorption. Only 3 of the 25 patients subjected to total gastrectomy absorbed over 92 per cent of dietary intake on all studies, and only 7 patients ever achieved normal absorption on even one study (without dietary adjuvants). The mean value for percentage absorption of dietary fat intake in this series of 59 studies was 81.7 per cent.

Fat absorption after total gastrectomy. The following factors affected fat absorption after total gastrectomy: (1) Dietary fat. In a limited number of individual studies, there are wide variations in the level of fat intake without other dietary changes. It can be seen from Figure 3, however, that the actual percentage absorption of dietary fat remains amazingly constant over a wide range of intake. (2) Dietary carbohydrate intake. Of 11 patients, more than 2 months after total gastrectomy, who were challenged with high carbohydrate intake while on a constant fat intake, 8 showed a decrease in fat absorption ranging from 4 to 50 per cent below the control values. The remaining 3 patients showed little change in fat absorption with this change in carbohydrate intake, but 2 of these 3 were among those without an absorption defect initially (Table III).[3] (3) Dietary adjuvants—hydrochloric acid. Administration of 25 cubic centimeters of 0.1 normal hydrochloric acid prior to meals produced an improvement in fat absorption in 5 of 8 patients after total gastrectomy and this was a frequent finding after partial gastrectomy also (Fig. 4). These data have been reported in greater detail in a separate report by Vanamee and associates on factors affecting postgastrectomy steatorrhea.

[2]Four studies were eliminated from these calculations for this reason.

[3]Four patients less than 2 months after operation were not included in this analysis as rapid changes in "adaptation" in this period seriously interfered with interpretation of data.

TABLE I.—CLINICAL AND METABOLIC DATA FROM 25 PATIENTS AFTER TOTAL GASTRECTOMY

Patient	Diagnosis	Age	Operation	Anastomosis	Time postoperative	CHO, gms.	Diet fat, gms.	N gms.	Stool fat, gms.	Fat absorption, per cent intake	Stool N gms.	Urinary N gms.	N absorption, per cent intake	Adj.	Body weight, kgm. Pre-illness	Pre-operative	Study
J K.	Gastric ulcer	34	Total	E-J	7 mos.	273	99.0	21.6	23.3	76.0	2.4	16.0	88.9		88.2	79.1	69.5
					2½ yrs.	195	89.0	26.0	12.8	85.0	2.6	24.5	90.0				
					4 yrs.	200	147.0	30.2	6.7	95.4	1.9	23.9	93.7				
					5 yrs.	205	103.9	26.8	1.3	98.7	1.7	27.6	93.7				68.6
						305	78.6	15.9	4.9	93.7	3.0	17.2	81.1				
					6 yrs.	356	76.0	—	2.3	97.0	—	—	—				
M.S.	Ca. stomach	77	Extended total	E-J	2 yrs.	156	35.6	—	6.1	82.0	—	—	—		56.8	45.9	43.2
					3½ yrs.	89	55.6	11.4	5.3	90.5	.4	9.8	96.5				40.9
						150	50.8	13.4	30.1	40.8	2.5	10.1	73.9				
J.M.	Ca. stomach	65	Extended total	E-J	4 yrs. 3 mos.	201	90.8	12.6	27.8	69.5	2.9	12.6	77.0		68.2	57.3	51.8
					8 yrs. 6 mos.	144	37.3	9.1	2.9	92.2	2.6	7.6	71.4				48.2
						234	85.1	11.7	21.1	75.2	3.1	6.6	73.5				
					9 yrs. 6 mos.	123	41.5	10.9	3.7	91.2	1.1	7.6	89.9				
						176	42.8	9.8	11.3	73.6	2.8	5.8	71.4				
						176	42.8	9.8	14.3	66.6	2.8	7.3	71.4	HCl			
A.B.	Leiomyomata stomach	41	Total	E-J	7 yrs. 6 mos.	145	30.3	8.5	5.2	82.7	1.7	9.3	80.0		47.7	43.2	43.2
						285	39.7	9.8	12.4	68.9	2.1	6.2	78.6				
I.K.	Ca. stomach	55	Extended total	E-J	3 yrs.	122	54.4	11.5	1.8	96.7	.8	11.1	93.0		69.1	60.0	56.8
						236	41.5	10.3	1.9	95.5	1.5	8.3	85.4				
J.M.	Ca. stomach	71	Extended total	E-J	7 yrs.	60	29.9	6.2	2.4	92.1	.6	9.7	90.3		84.1	75.9	78.6
						164	45.5	8.0	2.2	95.1	1.7	9.0	78.8				
E.T.	Ca. stomach	79	Extended total	E-J	7 yrs.	90	38.7	8.4	3.5	90.9	1.1	7.9	86.9		72.7	63.6	52.3
						158	35.0	8.4	7.3	79.1	2.6	6.0	69.0				
						158	35.0	8.4	2.6	92.6	3.4	5.5	59.5	HCl			
S.B.	Ca. stomach	70	Total	E-J	8 yrs.	130	69.0	15.0	4.5	93.5	3.5	8.9	76.7		65.9	59.1	49.1
						225	68.6	12.5	11.2	83.7	3.1	8.1	75.2				
						225	68.5	12.5	11.0	84.0	3.3	7.7	73.6	HCl			
G.G.	Leiomysarcoma of stomach	57	Total	E-J	5 yrs.	116	62.8	13.2	2.3	96.3	1.8	9.9	86.4		68.2	67.3	40.0
						211	52.5	11.8	4.4	91.6	2.0	9.8	83.1				
						211	52.5	—	2.4	95.4	—	—	—	HCl			
J.J.	Ca. stomach	61	Total	E-J	6 yrs.	—	147.0	12.1	7.9	94.6	2.2	5.1	81.2			60.0	68.2
M.N.	Ca. stomach	65	Extended total	E-J	4 yrs.	137	46.5	10.2	9.6	79.3	1.5	11.9	85.3		63.6	53.2	51.4
						231	53.7	12.6	7.6	85.8	1.6	8.4	87.3				
						231	53.7	12.6	3.3	93.9	1.9	9.5	84.9	HCl			
B.M.*	Benign ulcer	39	Total	E-J	2 yrs.	—	72.3	10.2	10.2	85.9	2.0	6.5	80.4		63.6	63.6	44.1
						—	72.3	10.2	10.0	86.2	2.0	6.5	80.4				

TABLE I.—CLINICAL AND METABOLIC DATA FROM 25 PATIENTS AFTER TOTAL GASTRECTOMY (Continued)

TABLE I.—CLINICAL AND METABOLIC DATA FROM 25 PATIENTS AFTER TOTAL GASTRECTOMY (Continued)

Patient	Diagnosis	Age	Operation	Anastomosis	Time postoperative	CHO, gms.	Diet fat, gms.	Diet N gms.	Stool fat, gms.	Fat absorption per cent intake	Stool N gms.	Urinary N gms.	N absorption per cent intake	Adj.	Body weight, kgm. Pre-illness	Body weight, kgm. Pre-operative	Body weight, kgm. Study
B.S.*	Leiomyosarcoma	50	Extended total	E-J	1 yr. 8 mos.	—	62.9	8.0	11.4	81.9	2.0	8.0	75.0		81.8		57.0
						—	62.9	8.0	18.2	71.0	1.8	7.4	77.5				
J.R.*	Cancer	68	Total	E-J	1 yr. 5 mos.	—	97.6	19.1	16.0	83.6	2.1	14.6	89.0		72.7	70.0	57.0
						—	172.9	11.2	33.2	81.2	1.8	12.1	84.0				
J.M.*	Cancer	63	Extended total	E-J	4 yrs.	—	90.8	12.6	19.6	78.2	2.9	10.9	77.0				51.0
F.Z.*	Cancer	58	Total	E-J	5 yrs.	—	92.8	14.9	12.8	86.2	1.9	12.5	87.2				64.0
M.N.	Ca. stomach	58	Extended total	Roux-Y	2 mos.	190	84.8	17.0	22.2	73.8	2.0	10.3	88.2		95.5	68.2	75.0
						329	148.4	26.5	32.5	78.1	3.9	14.1	85.3				
					6 mos.	348	172.9	29.0	28.4	83.6	3.4	24.4	89.3				81.4
M.S.	Ca. stomach	62	Extended total	Roux-Y	1 mo.	116	20.9	4.1	7.3	64.9	2.4	2.2	41.5		63.6	53.6	47.7
					4 mos.	138	17.6	5.4	5.9	66.2	1.3	3.4	75.9				43.2
						183	56.7	8.6	13.3	76.5	2.4	4.5	72.1				
						183	56.7	8.6	11.3	80.0	2.6	4.0	69.8	HCl			
J.F.	Ca. stomach	59	Extended total	Roux-Y	13 mos.	152	56.0	11.2	6.4	88.3	1.4	10.5	87.5		80.0	70.5	80.9
						279	60.0	14.5	18.0	70.0	3.1	7.4	78.6				
A.B.	Ca. stomach	61	Total	Roux-Y	2 wks.	106	54.9	11.8	28.0	50.8	5.2	5.0	55.9		72.7	61.8	51.4
						187	76.0	13.4	27.6	63.7	7.0	4.2	47.8				
						187	76.0	—	21.3	72.0	—	—	—	HCl			
H.B.	Ca. stomach	81	Total	Roux-Y (with "pouch")	2 mos.	119	51.9	9.8	6.0	88.4	2.5	5.6	74.5		84.1	77.7	70.9
						212	42.5	7.1	5.2	87.8	2.3	7.6	67.6				
						212	42.5	7.1	5.1	88.1	3.0	4.0	49.3	HCl			
N.F.*	Lymphosarcoma	47	Total	E-D	4 mos.	—	84.8	15.5	28.6	67.5	2.3	12.9	85.2		72.7	59.1	58.5
						—	84.8	15.5	27.8	67.2	3.0	12.3	80.6				
						—	84.8	15.5	20.5	75.8	2.5	12.3	83.9				
M.A.	Ca. stomach	52	Total	E-D	2 mos.	—	89.0	19.7	9.8	88.9	0.5	13.9	97.4		63.6	63.6	47.7
						—	88.5	10.2	28.5	67.8	2.5	10.2	72.0				
M.H.	Ca. stomach	39	Extended total	E-D	2 mos.	—	89.8	11.8	20.1	78.0	2.0	6.6	83.1		52.3	44.5	33.2
I.R.	Ca. stomach	60	Total (plus transverse colon)	Longmire	3 mos.	—	89.6	12.3	12.7	85.8	2.1	9.4	82.9			45.0	45.4
						—	46.9	12.7	7.3	84.4	1.8	8.5	85.8				

*Patients previously reported by Schwartz, Bodansky, and Randall.

TABLE II.—CLINICAL AND METABOLIC DATA FROM 17 PATIENTS AFTER SUBTOTAL GASTRECTOMY

Patient	Diagnosis	Age	Operation	Anastomosis	Time Postoperative	CHO, gms.	Diet fat, gms.	N gms.	Stool fat, gms.	Fat absorption, per cent intake	Stool N gms.	Urinary N gms.	N absorption, per cent intake	Adj.	Body weight, kgm. Pre-illness	Pre-operative	Study
E.S.	Ca. stomach	50	Proximal subtotal	E-G	2 yrs. 10 mos.	94	44.3	7.3	4.3	90.3	1.6	3.0	78.0		56.8	53.6	40.9
						232	53.6	10.1	17.5	67.3	1.6	7.6	84.2				
						94	46.2	8.0	4.4	90.4	1.0	6.8	87.5				
H.T.	Ca. stomach	67	Proximal subtotal	E-G	1 mo.	87	35.2	8.8	2.5	92.8	2.9	5.7	67.0		78.2	74.5	63.4
						195	34.6	8.7	8.6	75.1	1.9	6.3	78.1				
						195	34.6	8.7	4.5	87.0	1.9	6.7	78.1	HCl			
W.R.	Duodenal ulcer	44	Subtotal	Bill. I	2 yrs.	—	102.4	13.4	4.2	95.9	1.2	13.4	91.0		66.8	66.8	52.3
						—	102.4	13.4	5.0	94.9	1.5	12.5	88.8				
T.C.	Duodenal ulcer	28	Subtotal	Bill. I	1 yr.	141	58.2	17.5	1.7	97.0	1.5	15.7	95.4		69.1	68.2	59.1
						276	74.7	16.6	3.3	95.6	3.0	14.8	81.9				
J.C.	Ca. stomach	66	Subtotal	Bill. II	15 days	135	43.4	9.1	11.0	74.7	1.7	4.4	81.3		—	—	—
					5 yrs. 3 mos.	91	62.2	14.0	6.5	89.6	1.8	11.9	87.1				
						180	56.6	14.3	4.9	91.4	1.7	11.0	88.1				
J.McC.	Duodenal ulcer	59	Subtotal	Bill. II	5 mos.	92	76.1	13.6	4.2	94.5	2.5	11.4	81.6		72.7	61.4	65.9
						147	100.4	13.7	5.1	94.9	2.3	10.6	83.2				
O.H.	Duodenal ulcer	53	Subtotal	Bill. II	6 yrs.	85	43.9	12.3	.4	99.1	.6	10.8	95.1		59.1	50.5	45.5
						227	45.8	9.5	2.5	94.5	1.7	6.5	82.1				
Y.S.	Lymphosarcoma stomach	55	Subtotal	Bill. II	1 yr. 7 mos.	—	80.0	13.6	3.6	95.0	2.4	11.8	82.4		61.4	54.5	45.5
B.S.	Gastric ulcer	50	Subtotal	Bill. II	6 yrs.	89	20.3	7.8	3.3	83.9	1.5	8.1	80.8		—	—	56.8
						237	48.1	11.3	5.1	89.5	1.7	9.5	85.0				
						237	48.1	11.3	1.9	96.0	1.6	11.0	86.8	HCl			
J.W.	Gastric ulcer	65	Subtotal	Bill. II	2 yrs.	103	63.7	13.2	.4	99.4	1.2	12.3	90.9		65.9	65.9	57.7
						262	94.4	15.4	9.0	90.5	1.9	12.0	87.7				
						262	94.4	15.4	8.0	91.6	2.1	11.7	86.4	HCl			
K.C.	Gastric ulcer	47	Subtotal	Bill. II	1 mo.	94	38.7	9.4	8.2	78.9	1.3	9.1	86.2		62.7	55.5	50.0
						154	52.1	9.1	8.2	84.3	1.4	8.9	84.6				
						154	52.1	9.1	2.8	94.7	1.3	7.9	85.7	HCl			
J.O'C.	Ca. stomach	66	Subtotal	Bill. II	10 mos.	135	72.0	12.5	3.9	94.5	1.4	9.6	88.8		72.3	72.3	50.9
						184	81.0	14.5	3.5	95.6	0.9	9.9	93.8	HCl			

TABLE II.—CLINICAL AND METABOLIC DATA FROM 17 PATIENTS AFTER SUBTOTAL GASTRECTOMY (Continued)

Patient	Diagnosis	Age	Operation	Anastomosis	Time Postoperative	CHO, gms.	Diet fat, gms.	N gms.	Stool fat, gms.	Fat absorption, per cent intake	Stool N gms.	Urinary N gms.	N absorption, per cent intake	Adj.	Body weight, kgm. Pre-illness	Pre-operative	Study
E.S.	Ca. stomach	50	Proximal subtotal	E-G	2 yrs. 10 mos.	94	44.3	7.3	4.3	90.3	1.6	3.0	78.0		56.8	53.6	40.9
						232	53.6	10.1	17.5	67.3	1.6	7.6	84.2				
						94	46.2	8.0	4.4	90.4	1.0	6.8	87.5				
H.T.	Ca. stomach	67	Proximal subtotal	E-G	1 mo.	87	35.2	8.8	2.5	92.8	2.9	5.7	67.0		78.2	74.5	63.4
						195	34.6	8.7	8.6	75.1	1.9	6.3	78.1				
						195	34.6	8.7	4.5	87.0	1.9	6.7	78.1	HCl			
W.R.	Duodenal ulcer	44	Subtotal	Bill. I	2 yrs.	—	102.4	13.4	4.2	95.9	1.2	13.4	91.0		66.8	66.8	52.3
						—	102.4	13.4	5.0	94.9	1.5	12.5	88.8				
T.C.	Duodenal ulcer	28	Subtotal	Bill. I	1 yr.	141	58.2	17.5	1.7	97.0	1.5	15.7	95.4		69.1	68.2	59.1
						276	74.7	16.6	3.3	95.6	3.0	14.8	81.9				
J.C.	Ca. stomach	66	Subtotal	Bill. II	15 days	135	43.4	9.1	11.0	74.7	1.7	4.4	81.3		—	—	—
					5 yrs. 3 mos.	91	62.2	14.0	6.5	89.6	1.8	11.9	87.1				
						180	56.6	14.3	4.9	91.4	1.7	11.0	88.1				
J.McC.	Duodenal ulcer	59	Subtotal	Bill. II	5 mos.	92	76.1	13.6	4.2	94.5	2.5	11.4	81.6		72.7	61.4	65.9
						147	100.4	13.7	5.1	94.9	2.3	10.6	83.2				
O.H.	Duodenal ulcer	53	Subtotal	Bill. II	6 yrs.	85	43.9	12.3	.4	99.1	.6	10.8	95.1		59.1	50.5	45.5
						227	45.8	9.5	2.5	94.5	1.7	6.5	82.1				
Y.S.	Lymphosarcoma stomach	55	Subtotal	Bill. II	1 yr. 7 mos.	—	80.0	13.6	3.6	95.0	2.4	11.8	82.4		61.4	54.5	45.5
B.S.	Gastric ulcer	50	Subtotal	Bill. II	6 yrs.	89	20.3	7.8	3.3	83.9	1.5	8.1	80.8		—	—	56.8
						237	48.1	11.3	5.1	89.5	1.7	9.5	85.0				
						237	48.1	11.3	1.9	96.0	1.6	11.0	86.8	HCl			
J.W.	Gastric ulcer	65	Subtotal	Bill. II	2 yrs.	103	63.7	13.2	.4	99.4	1.2	12.3	90.9		65.9	65.9	57.7
						262	94.4	15.4	9.0	90.5	1.9	12.0	87.7				
						262	94.4	15.4	8.0	91.6	2.1	11.7	86.4	HCl			
K.C.	Gastric ulcer	47	Subtotal	Bill. II	1 mo.	94	38.7	9.4	8.2	78.9	1.3	9.1	86.2		62.7	55.5	50.0
						154	52.1	9.1	8.2	84.3	1.4	8.9	84.6				
						154	52.1	9.1	2.8	94.7	1.3	7.9	85.7	HCl			
J.O'C.	Ca. stomach	66	Subtotal	Bill. II	10 mos.	135	72.0	12.5	3.9	94.5	1.4	9.6	88.8		72.3	72.3	50.9
						184	81.0	14.5	3.5	95.6	0.9	9.9	93.8	HCl			

TABLE II.—CLINICAL AND METABOLIC DATA FROM 17 PATIENTS AFTER SUBTOTAL GASTRECTOMY (Continued)

Patient	Diagnosis	Age	Operation	Anastomosis	Time postoperative	CHO, gms.	Diet fat, gms.	N gms.	Stool fat, gms.	Fat absorption, per cent intake	Stool N gms.	Urinary N gms.	Urinary absorption, per cent intake	Adj.	Body weight, kgm. Pre-illness	Body weight, kgm. Pre-operative	Body weight, kgm. Study
J.O'C.	Ca. stomach	66	Subtotal	Bill. II	10 mos.	135	72.0	12.5	3.9	94.5	1.4	9.6	88.8		72.3	72.3	50.9
						184	81.0	14.5	3.5	95.6	0.9	9.9	93.8	HCl			
E.G.	Duodenal ulcer	57	Subtotal	Bill. II	8 yrs.	91	36.7	9.1	1.8	94.9	1.3	4.5	85.7		62.7	62.7	47.0
						206	35.4	9.3	3.7	89.6	1.7	4.5	81.7				
						206	36.3	10.0	.8	97.8	1.6	4.6	84.0				
W.B.S.	Duodenal and gastric ulcer	61	High subtotal	Bill. II	7 yrs.	—	85.6	—	6.6	92.3	—	—	—		—	—	—
J.G.	Duodenal ulcer	53	Subtotal	Bill. II	2 yrs. 9 mos.	96	54.2	12.9	1.8	96.8	1.4	11.3	89.9		58.2	52.7	46.4
						170	56.8	12.4	.9	98.5	0.5	10.2	96.0				
C.B.	Ca. stomach	51	Subtotal	Bill. II	3 mos.	—	46.6	13.6	9.3	80.2	1.5	10.4	89.0		51.8	51.8	42.3
J.A.	Ca. stomach	66	Subtotal with distal pancreas	Bill. II	4 mos.	—	88.0	14.5	11.6	88.0	1.1	10.6	92.4		77.3	60.5	52.3
						—	88.0	14.5	15.6	82.0	1.7	11.2	88.3				
						—	88.0	14.5	9.5	89.0	1.6	12.3	89.0				

Fat absorption after subtotal gastrectomy. The relationship between dietary intake of fat and the fecal fat in 34 studies of 17 patients after subtotal gastrectomy is demonstrated in Figure 5. The regression line for these data is $y = 0.3 + .10x$ ($r = .58$; $P < .01$). The mean value for fat absorption for the subtotal gastrectomy group was 90 per cent. Eleven patients of this group of 17 were above our arbitrary lower limit of normal of 92 per cent fat absorption on at least one study. Three of these patients had no absorptive defect on low carbohydrate intake, but an absorption defect became apparent on higher carbohydrate intake.

NITROGEN METABOLISM

Analysis of the protein metabolism of patients can be carried out in greater detail than fat metabolism, since total excretion of nitrogen can be measured by combining urinary with fecal nitrogen loss. By this means over-all balance data may be obtained in addition to data on alimentary absorption.

Protein absorption and metabolism after total gastrectomy. The data comparing total protein intake (expressed as nitrogen) with fecal nitrogen loss are charted graphically in Figure 6. The studies in which hydrochloric acid produced a change have been omitted from these calculations, leaving 57 studies for statistical analysis. Although the correlation coefficient of the regression equation ($y = 1.2 + .083x$) is significant at the 1 per cent level ($r = .44$), there is marked variability in these data, and this fact is readily apparent on inspection of the graph. Data on fecal nitrogen excretion in normal subjects reported by Forsyth and associates are also represented in Figure 6 by the dotted regression line.

Of even greater interest, however, is the relationship between nitrogen intake and total nitrogen excretion in the 25 totally gastrectomized patients (Fig. 7). Treatment of these data has given the regression line, $y = 32 + .81x$ ($r = .91$; $P < .01$) where y represents total combined fecal and urinary

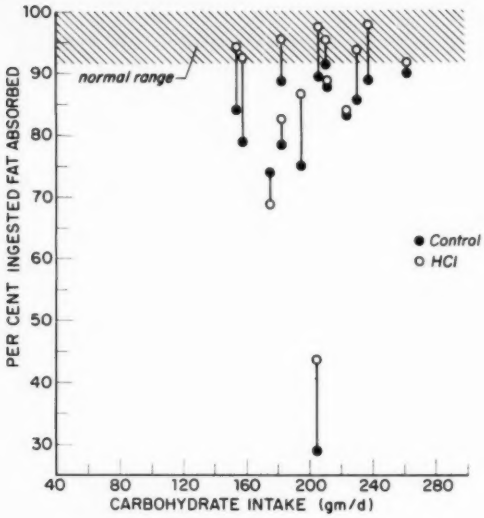

FIG. 4.

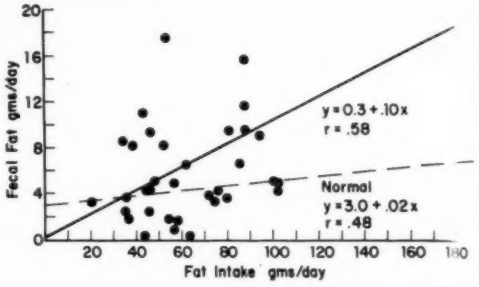

FIG. 5.

FIG. 4. Effect of administration of hydrochloric acid (25 c.c. 0.1N) before meals on fat absorption after subtotal and total gastrectomy in 13 patients with a defect in fat absorption.

FIG. 5. Relationship between fat intake and fecal fat in 17 patients after subtotal gastrectomy (34 studies).

nitrogen excretion and x the nitrogen intake, both expressed as milligrams per kilogram of body weight per day. This relationship demonstrates an increased nitrogen requirement in these patients as will be discussed subsequently.

Factors affecting nitrogen metabolism. Carbohydrate intake.—Metabolic data from 10 patients subjected to variation in carbohydrate intake while on constant nitrogen intake are shown in Figure 8. There was a decrease in absorption of nitrogen in all but 1 patient after increasing the dietary carbohydrate, and this decrease in absorption varied from 1.4 to 22.6 per cent of the dietary intake. The mean decrease in absorption in this group of 10 patients was 9.4 per cent. It would appear that the effect of increasing carbohydrate in the diet was similar with protein to that described in our fat absorption studies. The effect of this change in carbohydrate intake on fat metabolism could not be evaluated, as there is no satisfactory method for collecting and measuring the end products of fat metabolism. By nitrogen balance studies, however, the net result of dietary changes on nitrogen metabolism could be evaluated (Table IV). Only 2 of the 10 patients had a shift toward a more negative balance when carbohydrate intake was increased, despite an increase in fecal losses. Actually, the mean change in balance per patient, was +2.1 grams of nitrogen per day.

Because of this change in nitrogen absorption noted with modification of carbohydrate intake, it is not feasible to study the

TABLE III.—EFFECT OF CARBOHYDRATE INTAKE ON FAT ABSORPTION AFTER TOTAL GASTRECTOMY*

Patients with abnormal fat absorption, <92 per cent	*Fat absorption, per cent* — *Low carbohydrate diet*	*High carbohydrate diet*	*Change in absorption*
M.S.	90.5	40.8	50.4 ↓
J.M.	91.1	73.6	17.5 ↓
A.B.	82.7	68.9	13.8 ↓
E.T.	90.9	79.1	11.8 ↓
M.N.	79.3	85.8	6.5 ↑
J.F.	88.3	70.0	18.3 ↓
Patients with normal fat absorption, >92 per cent			
J.K.	98.7	93.7	5.0 ↓
I.K.	96.7	95.5	1.2 ↓
J.M.	92.1	95.1	3.0 ↑
S.B.	93.5	83.7	9.8 ↓
G.G.	96.3	91.6	4.7 ↓

Fat intake constant while carbohydrate intake varied.
*Four patients 2 months postoperative (H.B., A.B., M.S., M.N.) were not included due to confusion produced by rapid "adaptation" occurring in this early period.

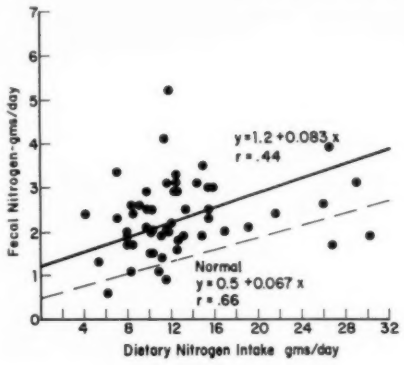

FIG. 6.

FIG. 6. Relationship between nitrogen intake and fecal nitrogen in 25 patients after total gastrectomy (57 studies). Normal data from Forsyth and associates shown in broken line for comparison.

FIG. 7. Relationship between nitrogen intake and total nitrogen excretion in 25 patients after total gastrectomy (57 studies).

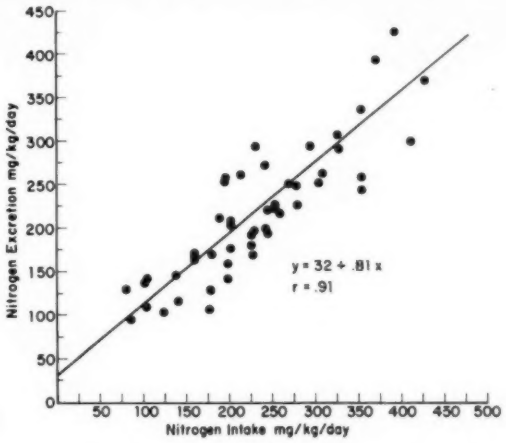

FIG. 7.

effects of variations in nitrogen intake on fecal excretion without maintaining a constant carbohydrate diet. Data fulfilling this requirement are insufficient to determine accurately the effect of variation of nitrogen intake on nitrogen absorption.

Dietary adjuvants.—In view of the increase in absorption of fat noted when hydrochloric acid supplements were administered prior to meals (25 c.c. 0.1 normal HCl), similar observations were made on nitrogen losses in 6 patients receiving such supplements. Contrary to the findings regarding fat absorption, there was a zero to 18 per cent decrease in nitrogen absorption while patients were receiving hydrochloric acid when compared with an otherwise identical metabolic period prior to this. The mean decrease in absorption for this group of 6 patients after total gastrectomy was 5.7 per cent. Study of the effect of this supplement on nitrogen balance showed no significant change in balance however (Table V).

Nitrogen metabolism after subtotal gastrectomy. Treatment of our data on 33 studies (without dietary adjuvants) of 17 patients after partial gastrectomy yielded the regression line, $y = -9 + .98x$ ($r = .88$; $P < .01$) where x = dietary intake of nitrogen as milligrams per kilogram per day and y = total nitrogen excretion as milligrams per kilogram per day. When dietary intake in grams was compared to fecal excretion in grams, the regression line $y = .16 + .125x$ ($r = .61$; $P < .01$) was obtained. Unfortunately, there were few data at lower levels of intake in this group which led us to consider the regression unreliable for this group. The patients subjected to subtotal gastrectomy were also a less homogeneous group than those after total gastrectomy because of the variations in extent of partial resection.

A study of nitrogen absorption on an increased carbohydrate diet in 8 patients of this subtotal gastrectomy group showed a mild decrease in absorption in 5 patients. These changes did not appear significant.

Relationship of body weight and nutritional status to metabolic data. It seemed reasonable to assume that a defect in fat or protein assimilation might contribute to the malnutrition observed in many patients after total gastrectomy. To evaluate this condition objectively, however, the relationship between fat absorption and body weight was considered. To achieve uniformity, the body weight at the time of the study was compared with the preoperative weight and

TABLE IV.—EFFECT OF CARBOHYDRATE INTAKE ON NITROGEN METABOLISM AFTER TOTAL GASTRECTOMY

	Nitrogen absorption, per cent			*Nitrogen balance, grams*		
Patient	*Low carbohydrate diet*	*High carbohydrate diet*	*Change in absorption*	*Low carbohydrate diet*	*High carbohydrate diet*	*Change in balance*
M.S.	96.5	73.9	22.6 ↓	+1.1	+ .8	−0.3
J.M.	89.9	71.4	18.5 ↓	+2.2	+1.2	−1.0
A.B.	80.0	78.6	1.4 ↓	−2.5	+1.5	+4.0
J.M.	90.3	78.8	11.5 ↓	−4.2	−2.7	+1.5
E.T.	86.9	69.0	17.9 ↓	−0.6	−0.2	+0.4
M.N.	85.3	87.3	2.0 ↑	−3.1	+2.6	+5.7
M.N.	88.2	85.3	2.9 ↓	+4.7	+8.6	+3.9
M.S.	75.9	72.1	3.8 ↓	+0.8	+1.8	+1.0
J.F.	87.5	78.6	8.9 ↓	−0.7	+4.1	+4.8
A.B.	56.0	48.0	8.0 ↓	+1.6	+2.3	+0.8
Means			9.4 ↓			+2.1

No decrease in nitrogen intake with increase in carbohydrate.

TABLE V.—EFFECT OF HYDROCHLORIC ACID ADMINISTRATION PRIOR TO MEALS (25 c.c. 0.1 N) ON NITROGEN METABOLISM AFTER TOTAL GASTRECTOMY (DIET CONSTANT)

	Nitrogen absorption, per cent			*Nitrogen balance, grams*		
Patient	*Control period*	*With HCl*	*Change in absorption*	*Control period*	*With HCl*	*Change in balance*
J.M.	71.4	71.4	0	+1.2	−0.2	−1.4
E.T.	69.0	59.5	9.5 ↓	−0.2	−0.5	−0.3
S.B.	75.2	73.6	1.6 ↓	+1.2	+1.6	+0.4
M.N.	87.3	84.9	2.4 ↓	+2.6	+1.1	−1.5
M.S.	72.1	69.8	2.3 ↓	+1.8	+2.1	+0.3
H.B.	67.6	49.3	18.3 ↓	−2.8	−0.4	+2.4
Means			5.7 ↓			No significant change in balance

this comparison was charted in terms of percentile gain or loss from the preoperative weight. Sufficient data were available on 21 patients after total gastrectomy to study this relationship. One value for fat absorption was used for each patient while on moderate fat and carbohydrate intake. Comparison between weight and fat absorption on 2 occasions in some patients gave a total of 26 correlations for the group of 21 patients. It can be seen from Figure 9 that there is very little positive correlation between the fat absorption data and the maintenance of body weight. Seven studies in 6 patients who achieved or exceeded preoperative weight at the time of study showed a mean fat absorption of 86.7 per cent. This was slightly higher than in the 19 studies of patients who did not achieve their preoperative weight at the time of study. It was found that the mean absorption in the 10 studies of 9 patients who were 1 to 15 per cent below preoperative weight was the same (82.4 per cent) as the mean absorption in the 9 studies of 9 patients 16 to 41 per cent below preoperative weight. When these same data were calculated, using the pre-illness weight as base line, in lieu of the preoperative weight, very similar findings were obtained. None of these patients actually exceeded their pre-illness weight at the time of the study period.

This report is not concerned with studies of the dumping syndrome, but additional comment is pertinent in regard to these body weight studies. Although after total gastrectomy the majority of these patients could be shown to have objective findings characteristic of the dumping syndrome by means of a test meal of hypertonic glucose, a much smaller proportion of patients complained of significant symptoms while on their usual diet. Six of these 21 patients after total gastrectomy did have severe dumping symptoms on their regular diet alone, and 3 of these patients were those 3 who had the greatest deficit in body weight in the entire group.

DISCUSSION

The observation that steatorrhea frequently follows total gastric resection has

been well established by many reports, including two from our own laboratory. These data on fecal fat excretion of 25 totally gastrectomized patients are quite similar to those from our initial report on 7 patients. The regression coefficients for both groups are identical (0.21) and comparison of the regression lines with that calculated for normal patients[4] from the data of Atwater and Benedict, Benedict and Milner, and Watt ($y=3.0+.02x$) shows a significantly increased fecal fat excretion after total gastrectomy.

The criteria used for considering an abnormality in fat excretion in an individual patient vary among authors. We chose 92 per cent absorption as the lower limit of normal from consideration of the 5 per cent mean value for fat excretion in patients without gastrointestinal disease (standard deviation 2.2 per cent).[4] Everson expressed the belief that, with diets containing less than 80 grams of fat per day, the fecal excretion of fat should be considered normal if under 10 grams per day. Patients on low fat intakes, however, seem to have approximately the same per cent absorption defect as when given diets with increased fat (Fig. 3). We have, therefore, adhered to the range of normal fat absorption as described. By utilizing this classification, 22 of 25 patients after total gastrectomy in this series had abnormal fat absorption on one or more blocks (88 per cent). Of Everson's 33 collected patients, 26 or 79 per cent, had abnormal absorption after total gastrectomy, although only 21 were considered abnormal by his own criteria. An additional 30 patients reported since that review by Polak and Pontes, Kelly, and Moreno showed an 80 per cent incidence (24 patients) of subnormal fat absorption after total gastrectomy. The range of mean absorption in these latter studies was 77 to 89 per cent. It can safely be said from all these data that the patient following total gastrectomy usually, but not always, exhibits

[4]Studies reviewed by Wollaeger and associates and by Schwartz and associates.

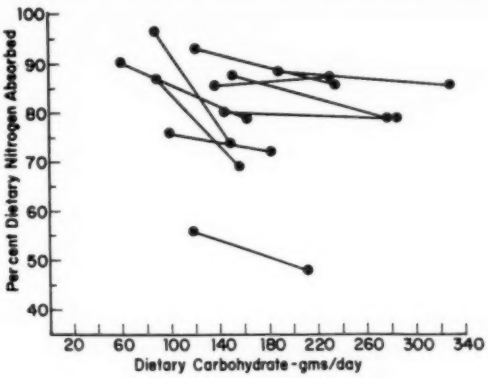

FIG. 8. Effect of change in carbohydrate intake on nitrogen absorption (as per cent of intake) in 10 patients after total gastrectomy. Data from Table V.

mild steatorrhea. The presence or degree of this abnormality seems unrelated to presence or absence of postprandial symptoms. This increased excretion is in the general range of 20 per cent of dietary fat in comparison with a 5 per cent figure for normal persons. The marked variations in fat absorption noted, even in the same patient, were definitely related to variations in carbohydrate intake in an appreciable number of patients.

The observation that there is a frequent decrease in fat absorption with increase in carbohydrate intake is of great interest in view of the established importance of carbohydrate intake in the "dumping syndrome." The mechanisms responsible for this effect on fat absorption may include decrease in bile production or enzyme production by the pancreas, or possibly, alterations in intestinal motility, but the exact cause must await further study. These changes and the improvement in postgastrectomy steatorrhea noted when hydrochloric acid, pancreatic supplements, or bile are given prior to meals have been discussed in detail in another report by Vanamee and associates.

A study of the factors that do not affect fat absorption is also interesting and of practical importance in management. When other dietary factors are relatively stable,

TABLE VI.—COMPARISON OF NITROGEN INTAKE-EXCRETION DATA OF PATIENTS AFTER TOTAL GASTRECTOMY WITH THAT OF NORMAL PERSONS

Data	*Regression equation*	*Correlation coefficient (r)**	*Excretion at zero balance, mgm./kgm./day*	*Calculated total nitrogen excretion at intakes producing zero nitrogen balance*	
				112 mgm./kgm./day	*168 mgm./kgm./day*
Present study (Total gastrectomy)	$y=32+0.81x$	0.91	168	123 (93–153)	168 (138–198)
Von Hoesslin (Normal patients)	$y=77+0.31x$	0.96	112	112 (93–131)	155 (136–174)
Beattie and associates. (Normal patients)	$6=27+0.76x$	0.90	112	112 (92–132)	155 (135–175)

*All significant at less than .01 level.

TABLE VII.—COMPARISON OF FECAL EXCRETION OF NITROGEN IN NORMAL PERSONS WITH FECAL EXCRETION IN PATIENTS AFTER TOTAL GASTRECTOMY

Data	*Regression equation*	*Correlation coefficient (r)**	*Fecal nitrogen at zero balance, gm./day*	*Calculated fecal nitrogen excretion at intakes producing zero nitrogen balance*	
				Normal 112 mgm./kgm./day	*Total gastrectomy 168 mgm./kgm./day*
Present study (Total gastrectomy)	$y=1.2+0.083x$	.44	1.83	24	33
Forsyth and associates (Normal subjects)	$y=0.5+0.067x$	.66	.95	16	20
	Comparison of normals with gastrectomized patients in regard to nitrogen excretion		Difference in fecal nitrogen excretion	8	13
			Difference in total nitrogen excretion (from Table II)	11	13

Differences in fecal excretion between groups at two levels of intake are compared with data from combined fecal and urinary excretion.
*Both significant at less than .01 level.

marked variations in the fat intake itself do not affect the per cent fat absorption to any significant degree. This laboratory finding is of great importance and can be effectively utilized in the nutritional management of such patients. The fecal fat loss can be offset by a moderate increase in fat intake since the per cent absorbed does remain constant.

Another factor which seems to have little effect on the degree of steatorrhea observed is the type of anastomotic reconstruction utilized after total gastrectomy. Most of the patients in the series had simple end-to-side esophagojejunostomy, and the data on fat absorption in this group ranges from 69 to 97 per cent. Patients with Roux-Y anastomosis did not demonstrate any difference from the former group in regard to fat absorption despite our clinical impression that this anastomosis was definitely followed by less severe postprandial symptoms than end-to-side esophagojejunal anastomosis. This observation is in agreement with the report of Kelly and associates. Esophagoduodenal reconstruction was utilized in only 3 patients but was not accompanied by any apparent difference in objective metabolic data on fat absorption, although this had been reported by others. Since only 1 patient in this series had a simulated "gastric pouch" of any type, no statement can be made regarding metabolic effects after this method of reconstruction. Limited data reported by Moreno show that patients with "pouch" reconstruction demonstrate no real metabolic difference from simpler procedures despite easier maintenance of satisfactory body weight. Limo-Basto, on the other hand, has presented data suggesting metabolic benefit from such procedures.

The cause of the steatorrhea after gastrectomy has been discussed in great detail in other reports. The loss of the reservoir and triturating function of the stomach, decreased stimulation and poor mixing of pancreatic and biliary secretions, and al-

terations or abnormalities in intestinal motility may all play some role in this mild abnormality of fat absorption. To these explanations one might now add the effect of dietary carbohydrate level as well as the role of intestinal *p*H.

Two aspects of the steatorrhea problem should be kept in mind from a practical clinical standpoint. The first is the relatively poor correlation noted between actual ability to maintain body weight after total gastrectomy and the degree of steatorrhea observed on metabolic study. This observation suggests that the defect in fat absorption usually contributes a minor role in the malnutrition. The second factor which should be appreciated is that the degree of steatorrhea noted in these patients is of a mild degree when compared with that noted after massive small bowel resection, sprue-like syndromes, and major pancreatic resection. Although the steatorrhea after total gastrectomy is of great interest from the physiologic and etiologic standpoint, the role of the steatorrhea is probably of less clinical significance than we previously imagined. A wonderful example is our patient, G. G., who 5 years after total gastrectomy demonstrated normal absorption of dietary fat (96.3 per cent) but was only able to maintain body weight at a level 41 per cent below her preoperative weight. In contrast to this is M. N., one of our best clinical results from the nutritional standpoint. He has exceeded his preoperative weight, continues to gain weight but demonstrates a fecal fat excretion of more than 20 per cent of his fat intake. These observations support the concept that post-gastrectomy nutrition is most closely related to the ability of the patient to tolerate adequate intake without disabling symptoms and not to the degree of steatorrhea.

The group of patients subjected to the subtotal gastrectomy were also found to have a decrease in fat absorption when compared to normal patients, but this defect was not as frequent or as severe as was seen after total gastrectomy. Most of the

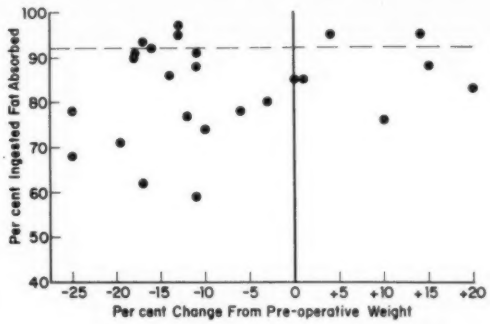

FIG. 9. Relationship between fat absorption (as per cent of intake) and body weight at time of study (as per cent of preoperative weight). These are 26 separate studies in 21 totally gastrectomized patients receiving moderate fat, moderate carbohydrate diet. (Patient G. G., with fat absorption 96.3 per cent of intake and body weight 41 per cent below preoperative weight, does not appear.)

factors generally considered to be responsible for the steatorrhea noted after total gastrectomy apply in part to patients subjected to partial gastrectomy so that these observations on fat absorption after subtotal gastrectomy are what one might expect.

Six of our group of 17 patients after subtotal gastrectomy were below the lower limit of normal fat absorption (92 per cent). In the group of 44 patients reviewed by Everson, 35 had abnormal fat absorption when the same criteria were used, but of the 18 cases reported since that time by MacLean and associates, Hayes, and Moreno, there was a 50 per cent incidence of defect in fat absorption. In general, the absorption of fat after partial gastrectomy is nearer the normal range than after total gastrectomy and is therefore of even less clinical importance.

As previously reported, 5 patients in the group that were studied on more than one occasion after total gastrectomy showed some improvement in fat absorption with the length of postoperative interval. When the per cent fat absorption was correlated with the postoperative time, there seemed to be a definite tendency for an improved fat absorption with longer period between

surgery and the metabolic study. In 11 patients who were studied at a time 2 years or more after total gastrectomy, the mean of the maximum fat absorption attained was 90.6 per cent. This minimal defect is of the same degree of magnitude as that seen in studies of most patients after partial gastrectomy. Actually, 7 of these 11 patients studied more than 2 years postoperatively reached normal range of fat absorption (92 per cent). It seems clear that although some patients do have significant steatorrhea after total gastrectomy, fecal fat losses become even less important after the patient has fully recovered and undergone a sufficient postoperative interval to become adjusted to his new gastrointestinal state.

Since optimum nutrition with maintenance of lean tissue mass is governed by absorption of protein, as well as utilization of this foodstuff, the over-all metabolism of nitrogen in these gastrectomized patients was of great interest. The relationship between fecal nitrogen and dietary nitrogen in normal patients has been shown by Forsyth and associates to have a definite relationship. Although there is some variability in the data, the same situation applies to our group of patients after total gastrectomy, but the fecal excretion of nitrogen is at a slightly higher level than in normal individuals. This finding might be considered a decrease in absorption of protein (as nitrogen) and such an impairment in absorption might have similar etiologic mechanisms to the mild steatorrhea described. The absorption of nitrogen was plotted against the absorption of fat in 57 individual studies, and the correlation coefficient for this relationship (.69)[5] showed a positive correlation between these two metabolic defects. Since the defects with each foodstuff are probably due to a multiplicity of factors, however, it is not possible to say that the defects in absorption were due exclusively to common etiologic mechanisms.

In contrast to the studies of fat metabolism, nitrogen lends itself to more adequate study in that total nitrogen excretion can be compared with total nitrogen intake. This relationship was compared with calculations by Schwartz from the data in normal patients previously reported by von Hoesslin and Beattie and associates. Both of these groups of normal patients were malnourished as a result of inadequate intake and were being repleted at the time of the study. Although the regression lines for these two groups of normal data are ostensibly different, it is of interest that the theoretic intake to produce zero balance in each of these normal groups was 112 milligrams of nitrogen per kilogram of body weight per day.[6] On the other hand, the intake and excretion at zero balance in our group of patients after total gastrectomy was somewhat higher than this: 168 milligrams of nitrogen per kilogram of body weight per day (See Table VI). The total nitrogen excretion at intakes producing zero nitrogen balance in both the normal patients and patients after total gastrectomy are recorded with a range of two standard deviations about these calculated excretion values. There was sufficient overlap in each of these calculations of total nitrogen excretion at both levels of intake to prevent a strong statement regarding a difference in nitrogen intake requirements for equilibrium. However, the nitrogen intake adequate for equilibrium in normal persons does appear generally insufficient for nitrogen equilibrium in totally gastrectomized patients, and there tends to be a negative balance in these patients who had total gastrectomy when they are on such an intake (Table VI).

The question arises as to whether the apparent difference in nitrogen requirement for equilibrium between the totally gastrectomized patients and normal patients is due to diminished intestinal absorption of nitrogen alone or to increased metabolic requirements also. For this reason; we calculated theoretic fecal nitrogen excretion as milligrams per kilogram per day at the in-

[5]P<.01.

[6]This was calculated by solving the regression equations for the point where x=y, or "zero balance."

takes producing zero nitrogen balance in each of these two groups. For these purposes, known body weights were utilized for the patients in our study and a mean body weight of 60 kilograms was assumed for the normal subjects reported by Forsyth and associates. Comparison of the fecal nitrogen excretion at these two intakes with the total nitrogen excretion at the same intakes reveals no increase in nitrogen excretion in patients after gastrectomy that cannot be attributed to excess stool nitrogen alone (Table VII). Since the absorptive defect in regard to nitrogen is not severe, a slight increase in protein intake can easily offset this defect in nitrogen absorption.

Factors we have recently shown to affect fat absorption also affect the absorption of protein (as nitrogen), but in a somewhat different manner. Increasing the carbohydrate in the diet reduces the absorption of nitrogen to some degree, just as with fat, but a study of the over-all effect of this dietary change actually reveals an increase in nitrogen retention, possibly due to increased calorie intake. This finding could hardly be considered disadvantageous from the nutritional standpoint. Hydrochloric acid supplements produce no significant change in nitrogen balance, but they do demonstrate a decrease in nitrogen absorption, a finding opposite to that noted with fat absorption. The reason for this apparently opposite effect on these two foodstuffs is not clear. Patients after partial gastrectomy had changes in nitrogen metabolism as described, but the diminished absorption of nitrogen was less striking than in patients after total gastrectomy.

A small but consistent excess loss of fat, protein, or calories due to diminished absorption can accumulate so as to contribute significantly to postgastrectomy malnutrition. All measurable defects in absorption, however, can be easily managed by a small appropriate increase in intake. This is a practical solution if symptoms after eating do not prevent a reasonable dietary intake. In our experience, the most acceptable diet in regard to postprandial "dumping" symptoms is the high protein, high fat, low carbohydrate, frequent feeding diet. This can provide sufficient calories and tends to produce symptoms to a lesser degree than diets containing a larger proportion of carbohydrate. Other measures which tend to minimize the dumping syndrome are of great importance in the management of some of these patients from the standpoint of nutrition. These include the maintenance of a normal blood volume, reclining after meals, and support of the psyche. Vitamin supplements, particularly vitamin B_{12}, are also important in the management of some of these patients. Despite rigid adherence to such a dietary plan, some patients after total gastrectomy will still have disabling symptoms and some degree of malnutrition. It has been our experience, however, that the majority of patients can be maintained in an adequate state of nutrition on this program.

SUMMARY

A series of 25 patients after total gastrectomy and 17 patients after subtotal gastrectomy were subjected to metabolic study.

1. The mean fat absorption after total gastrectomy was 81.7 per cent of intake (normal range is 92 to 100 per cent), but there was much variation between patients. The per cent absorption of dietary fat in individual patients was completely unaffected by variations in fat intake, generally decreased by increasing dietary carbohydrate, and usually increased when hydrochloric acid supplements were administered.

2. Protein absorption was also decreased after total gastrectomy. Increasing the dietary carbohydrate reduced nitrogen absorption, but total retention of nitrogen was slightly increased as judged by urinary nitrogen measurements. Hydrochloric acid supplements decreased protein absorption slightly, in contrast to the findings with fat absorption, but this did not cause a negative nitrogen balance.

3. Comparing the mean dietary protein intake required to achieve "zero balance" after total gastrectomy with similar calculations from groups of normal subjects demonstrated a definite increase in dietary nitrogen requirement for these patients.

4. Metabolic studies of patients after subtotal gastrectomy showed similar, but less striking, variations in both fat and nitrogen metabolism.

5. Comparison of our metabolic data with body weight studies in the same patients showed a poor correlation between nutritional state and the observed absorption defects. The most important factor in adequate nutritional maintenance seemed to be the ability to control postprandial symptoms sufficiently to allow adequate intake.

6. With careful dietary management the majority of these patients could be maintained in adequate nutritional state, and this fact would seem to justify continued performance of total gastrectomy, when indicated, for cancer of the stomach.

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AN EXPERIMENTAL STUDY OF THE DIAGNOSIS OF MESENTERIC INFARCTION

KAREL B. ABSOLON, M.D., SISTER VICTORINE LONG, M.S., and SAMUEL W. HUNTER, M.D., F.A.C.S., Minneapolis, Minnesota

DESPITE THE ADVANCES MADE in the treatment of intestinal obstruction and thromboembolic disease, acute mesenteric vessel occlusion remains the most deadly of all causes of intestinal obstruction. A variety of clinical manifestations is found, ranging from asymptomatic cases and those of recurrent episodes of abdominal pain or intestinal malabsorption to the other extreme of acute irreversible bowel infarction due to acute occlusion of the mesenteric artery, vein, or both.

Delay in diagnosis of acute mesenteric vessel obstruction is an important cause of the high mortality. The x-ray finding of small and large bowel distention, either mechanical or paretic in character, which stops at the transverse colon is significant diagnostically, but an extreme absence of intestinal gas is commonly found. Barium swallow will reveal a remarkable retention in the affected loops which show less distention than in mechanical obstruction; but the advisability of this examination must be questioned. Peritoneal tap will yield bloody fluid in some cases of mesenteric vein thrombosis but is rarely positive with acute mesenteric artery occlusion. Severe abdominal pain and shock with associated cardiovascular disease should suggest embolic mesenteric artery obstruction. However, some patients with mesenteric infarction have only minor symptoms during the initial stages of the disease so that the differential diagnosis may present formidable problems.

Resection of the necrotic bowel is the most common form of therapy. The direct surgical attack on the mesenteric artery by embolectomy, thrombarterectomy, and bypass grafts are possible only as long as the intestine retains its recuperative power. Propagation of an initially limited embolic and thrombotic process is another consideration. Early diagnosis is, therefore, essential. Aortography may delineate the mesenteric artery obstruction and demonstrate its collateral channels; but it does not appear to be a suitable examination for severely ill patients.

Measuring the enteric blood flow is the central point of inquiry. Intravenous injection of I^{131} labeled human serum albumin and approximation of the intestinal and mesenteric blood flow by recording the radioactivity determined by a collimated scintillation counter, externally placed over the abdomen, offered itself as a feasible approach. Similar techniques have been pre-

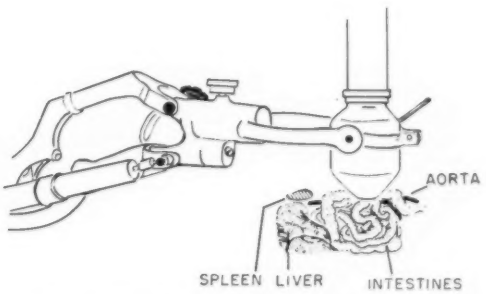

FIG. 1. Drawing of radioisotope recording apparatus in position.

From the Department of Surgery, University of Minnesota, and the Cardiovascular Research Laboratory, St. Joseph's Hospital, St. Paul, Minnesota.

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TABLE I.—CONTROL SERIES (GROUP 1)

Dog No.	Weight, lbs.	Total RISA i.v., μc.	RISA per lb.	Maximum count, ×10² 5–12 Sec.	20 Sec.	30 Sec.	60 Sec.
1	14	5	.35	255	150	165	165
2	30	5	.16	260	135	140	140
3	15	5	.33	200	130	130	130
4	14	5	.35	280	190	200	210
5	19	5	.26	225	145	160	155
6	23	5	.21	200	130	120	100
7	9	5	.55	225	130	125	125
8	31	5	.16	140	80	70	75
9	15	5	.33	145	85	90	95
Average	18.8	5	.30	214.4	130.5	133.3	132.7

RISA, I^{131} labeled human serum albumin.

TABLE II.—MESENTERIC ARTERY LIGATION (GROUP 2)

Dog No.	Weight, lbs.	Total RISA i.v., μc.	RISA per lb.	Maximum count, ×10² 5–12 Sec.	20 Sec.	30 Sec.	60 Sec.
1	14	5	.35	120	130	140	160
2	16	5	.31	120	130	160	160
3	16	5	.31	160	145	145	150
4	15	5	.33	115	120	120	125
Average	15.2	5	.32	128.7	131.2	141.2	148.7

TABLE III.—MESENTERIC VEIN LIGATION (GROUP 3)

Dog No.	Weight, lbs.	Total RISA i.v., μc.	RISA per lb.	Maximum count, ×10² 5–12 Sec.	20 Sec.	30 Sec.	60 Sec.
1	20	5	.25	30	100	105	135
2	15	5	.33	25	75	90	120
3	19	5	.26	30	90	105	105
4	13	5	.38	20	50	70	75
Average	16.7	5	.30	26.2	78.7	92.5	108.7

TABLE IV.—SIMULTANEOUS MESENTERIC ARTERY AND VEIN LIGATION (GROUP 4)

Dog No.	Weight, lbs.	Total RISA i.v., μc.	RISA per lb.	Maximum count, ×10² 5–12 Sec.	20 Sec.	30 Sec.	60 Sec.
1	21	5	.23	50	55	60	60
2	21	5	.23	150	145	140	135
3	13	5	.38	20	25	45	50
4	17	5	.29	20	30	40	50
5	27	5	.18	20	70	80	75
Average	19.8	5	.262	52.0	65.0	73.0	74.0

viously applied for circulation studies in congenital heart disease and peripheral vascular disease. Experiments were devised in dogs in an attempt to establish the usefulness of such a technique for diagnosis of mesenteric infarction.

METHOD AND MATERIALS

Mongrel dogs, weighing 9 to 31 pounds, were anesthetized with pentobarbital sodium administered intravenously and positioned for midline celiotomy. The right external jugular vein was cannulated and a polyethylene catheter was inserted into the superior vena cava. The abdomen was entered through a midline incision; the pedicle of the small bowel mesentery was exposed, and the mesenteric artery and vein were dissected. The animals were divided into the following four groups: group 1 (9 dogs) was a control group on which a sham operation was performed; group 2 (4 dogs) included those in which the mesenteric artery was ligated; group 3 (4 dogs) comprised those in which the mesenteric vein was ligated; in group 4 (5 dogs) both the mesenteric artery and vein were ligated simultaneously. After the surgical procedure was terminated, the abdominal incision was closed in layers.

Two hours after the operation, each animal was placed in a right lateral position, and a scintillation detector with a flat-field head attachment was located on the side of the abdomen distal to the thoracic cage and anterior to the vertebral column (Fig. 1). After rapid injection of 5 microcuries of I^{131} labeled human serum albumin in 5 milliliters of saline via the vena cava the ensuing radioactivity of the abdomen was traced with a rectilinear recording milliammeter attached to a precision ratemeter.

RESULTS

Group 1 (Table I, Fig. 2). As previously mentioned, a sham surgical procedure was done on these 9 dogs. The average weight of the group was 18.8 pounds (9 to 31) and the average dose of I^{131} labeled human serum albumin was .30 microcuries per pound (.16 to .55). A precipitous rise of radioactivity was noted in 3 to 5 seconds after intravenous injection, reaching a sharp maximum peak in 5 to 12 seconds. This was followed by a rapid decrease of radioactivity with a "negative" notch at 8 to 25 seconds before reaching equilibrium.

Group 2 (Table II, Fig. 3). The mesenteric artery was ligated in 4 dogs. The

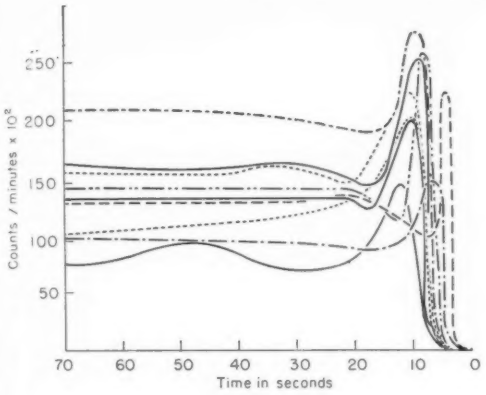

FIG. 2.

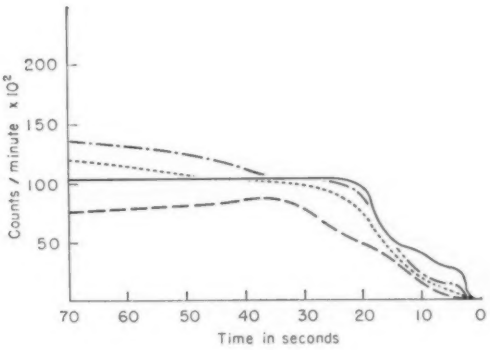

FIG. 4.

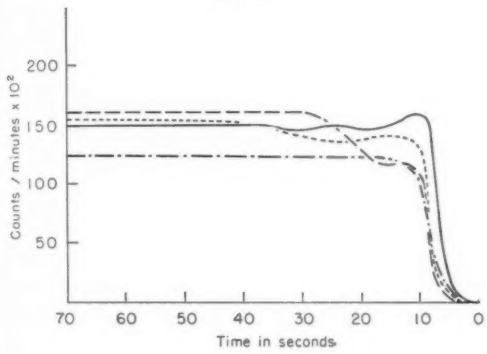

FIG. 3.

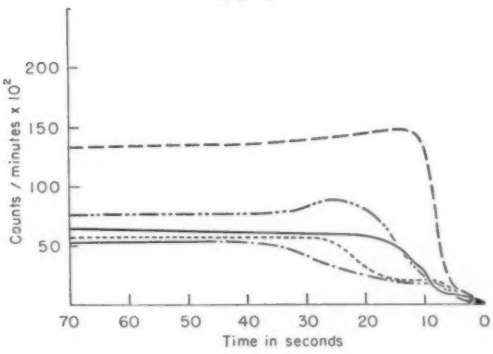

FIG. 5.

FIG. 2. Patterns recorded in normal dogs—group 1 (control group).
FIG. 3. Patterns recorded after mesenteric artery ligation—group 2.
FIG. 4. Patterns recorded after mesenteric vein ligation—group 3.
FIG. 5. Patterns recorded after simultaneous mesenteric artery and vein ligation—group 4.

average weight was 15.2 pounds (14 to 16) and the average dose of I^{131} labeled human serum albumin .32 microcuries per pound (.31 to .35). The rise in radioactivity began in 5 to 8 seconds after intravenous injection, reached a maximum in 10 seconds, and leveled off. In 1 animal the initial rise, slightly above the subsequent levels, was followed by a shallow negative curve.

Group 3 (Table III, Fig. 4). The mesenteric vein was ligated in 4 dogs. The average weight was 16.7 pounds (13 to 20) and the dose of I^{131} labeled human serum albumin .30 microcuries per pound (.25 to .38). Three to 8 seconds after injection of the radioactive material a slow rise in radioactivity was registered which continued for 20 to 35 seconds. From this point on, in 2 animals a further slower increase occurred, in one there was a leveling off and in the other a decrease.

Group 4 (Table IV, Fig. 5). The mesenteric artery and vein were simultaneously ligated in 5 dogs. The average weight of the animals was 19.8 pounds (13 to 27) and the average dose of I^{131} labeled human serum albumin .26 microcuries per pound (.18 to .38). A very slow rise of radioactivity over the abdomen was noted in 4 dogs, reaching a

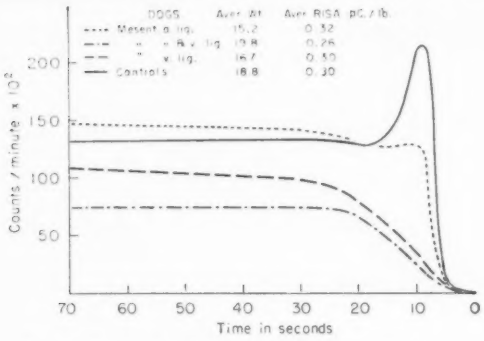

FIG. 6. Comparison of averages in groups 1 to 4.

maximum at 17 to 40 seconds after injection and maintaining the same level thereafter. In the fifth animal the initial rise was more rapid, reaching a maximum at 10 seconds after I^{131} labeled human serum albumin injection and then leveling off at this point.

The pathologic changes noted after ligation of the mesenteric vessels were localized in the jejunum and ileum to approximately 5 centimeters from the ileocolic juncture. After ligation of the mesenteric artery multiple blanched areas and hyperperistalsis developed. Almost immediately after the mesenteric vein was ligated, the bowel turned purple-blue and became distended and congested. Upon simultaneous ligation of the mesenteric artery and vein, two different types of changes were noted. When the ligature was tied rapidly, the picture was similar to that after mesenteric artery occlusion; slower obliteration of the vessels caused changes like the mesenteric vein occlusion. The vein undoubtedly was obstructed under such circumstances while inflow through the mesenteric artery continued for an instant.

COMMENT

Characteristic radioactivity curves were obtained over the abdomen in normal animals after rapid intravenous injection of a bolus of I^{131} labeled human serum albumin. The initial peak in such dogs appeared to depend on the rapidity of injection rather than on the dose of the radioactive material. After the mesenteric artery was ligated, a radioactivity rise almost as rapid as in the controls was noted, but the initial peak was absent. Ligation of the mesenteric vein caused a slower radioactivity rise over the abdomen than in the previous two groups (Fig. 6). It was thus possible to differentiate this experimental pathologic condition not only from the normal status but from the dogs with mesenteric artery ligations as well. Upon simultaneous mesenteric artery and vein ligation, curves were obtained in 4 animals similar to those after mesenteric vein ligation. One resembled that found after mesenteric artery ligation. This difference might well be due to the particular pathologic condition created as mentioned previously.

The more rapid rise of radioactivity over the abdomen after mesenteric artery ligation than after mesenteric vein ligation was difficult to explain. Interposition of the bulky congested loops after vein ligation between the scintillation counter and normal perfused tissues in the latter group is a factor. In addition, vasospasm and hypotension associated with vein obstruction might have amplified this phenomenon. At any rate it was a consistent finding. The liver, spleen, and aortic blood flow did not interfere with these determinations.

Due to the simplicity of this test, clinical application is warranted. The procedure may be done at the patient's bedside with minimal discomfort to him. Whether or not such a clear differentiation will be possible in humans as in the experiment must await clinical trial. By improving the diagnostic accuracy of mesenteric artery occlusion, direct attack on the diseased vessel by corrective procedures such as embolectomy, thrombarterectomy, and graft replacement should be feasible in a larger number of patients. Restoration of a more physiologic status than can be obtained with extensive bowel resection should be realized by such means.

Further documentation such as Derrick's, aided by a simple screening diagnostic technique as described, may prove abdominal pain and undernutrition of the elderly to be the most common manifestation of mesenteric vascular occlusive disease of varying degrees amenable to surgical correction.

SUMMARY

A new technique to diagnose mesenteric infarction was developed. Radioactivity determination over the abdomen in normal dogs showed characteristic curves after intravenous injection of I^{131} labeled human serum albumin. Such curves markedly differed from those obtained in dogs after mesenteric artery and vein ligation. The diagnostic dilemma in mesenteric infarction was discussed, and the therapeutic implications of improved diagnosis were emphasized.

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INFLUENCE OF RENAL DENERVATION UPON RENAL BLOOD FLOW

J. G. JONTZ, M.D., C. S. SU, M.D., H. B SHUMACKER, JR., M.D., F.A.C.S., and G. BOUNOUS, M.D., Indianapolis, Indiana

ONE HUNDRED YEARS AGO Claude Bernard observed that section of the splanchnic nerves of an anesthetized animal resulted in an increased flow of urine. Since then, a number of laboratory and clinical investigations have been carried out designed to elucidate the relationship between innervation of the kidney and renal hemodynamics and function. The problem has been approached by two general methods. Some have studied the effect of stimulating the renal nerves. The monograph of Trueta and his associates deals to a large extent with this approach to the problem. Others have continued to work along this line. The second method is the study of renal hemodynamics after acute or chronic renal denervation.

The present investigation was undertaken in order to study the effect of unilateral thoracolumbar sympathectomy and splanchnicectomy upon renal blood flow.

MATERIALS AND METHODS

Adult healthy mongrel dogs ranging in weight from 12 to 17 kilograms were used. They were anesthetized by the intravenous administration of thiopental sodium. An endotracheal tube was passed, and respirations were maintained with intermittent positive pressure oxygen administered by a mechanical respirator. An intercostal incision through the ninth intercostal space was made and the sympathetic chain was mobilized from the fourth thoracic ganglion down to the diaphragm. A muscle-splitting incision was then made just below the costal margin, and the dissection was carried retroperitoneally until the lumbar sympathetic chain was identified. The thoracolumbar sympathetic chain from the fourth thoracic ganglion down to and including the fourth lumbar ganglion was excised along with the greater, lesser, and least splanchnic nerves. Studies of renal blood flow were made from 14 to 21 days later.

Group 1. In these animals, a modification of a method which has proved satisfactory to us for the direct measurement of total renal blood flow (4) was utilized. The vena cava and both renal veins were exposed through a right flank incision. The ovarian or spermatic veins were ligated. Umbilical tapes were placed about the vena cava both above and below the points of entry of the renal veins. A No. 14 French catheter was inserted into the left femoral vein and passed cephalad in the vena cava until its proximal end was a few centimeters above the renal vein. This catheter was constructed with multiple perforations in its lower portion so that when the vena cava was occluded below the renal vein the infrarenal vena caval blood would drain freely into the unobstructed suprarenal portion of the inferior vena cava. A 5/16 inch plastic catheter was inserted into the right femoral vein and passed cephalad until its proximal end lay in the vena cava directly between the two renal veins. When the umbilical tapes were tightened about the vena cava above and below the point of entry of the renal veins, blood coming from the renal veins flowed freely through this catheter into a graduated burette. Blood was returned from the burette

From the Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana.

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into the right jugular vein by means of a sigmamotor pump which was adjusted so that the blood was returned to the body at the same rate at which it flowed into the burette. Each animal was given 1.5 milligrams per kilogram of heparin intravenously prior to the insertion of the catheters. The burette and tubing were filled with heparinized blood from a donor animal before the beginning of each experiment. The burette was positioned a few centimeters below the level of the operating table so that the renal veins were not collapsed and yet drained freely by gravity. By stopping the pump one could time the flow of a measured amount of blood into the burette and thus calculate renal blood flow in cubic centimeters per kilogram per minute. Flow from each kidney was obtained by cross-clamping one of the renal veins with a noncrushing vascular clamp for a few moments while the flow from the other kidney was recorded. By utilizing this method, renal blood flow from the right and left kidneys of 8 animals was measured. All studies were carried out over a 30 minute period, and all flow values were recorded when the animal's blood pressure was at a normotensive level. Blood pressure was measured by means of a mercury manometer in a femoral artery. The animals were sacrificed at the end of the experiment.

Group 2. In order to obviate the possible objection to the method used in group 1, namely, the momentary obstruction of blood flow through one renal vein, another method was utilized. Animals in this group had undergone unilateral renal denervation in the same manner as previously described. They were prepared for measurement of renal blood flow in a similar way. A 5/16 inch catheter was then inserted into the right femoral vein and passed directly into the right renal vein. A ligature was placed about the vein and the indwelling catheter so that all the renal venous blood from that kidney drained freely into a burette by gravity (Fig. 1). Another catheter of the same size was inserted into the left jugular vein, passed down through the superior vena cava, the right atrium, and the inferior vena cava into the left renal vein. A ligature was similarly placed about the vein and the indwelling catheter. This catheter permitted drainage of the left renal venous blood into a second burette. The blood from each burette was delivered by pump back into the right jugular vein. By using separate burettes simultaneous measurements of renal flow from each kidney could be made. All experiments were carried out over a period of 30 minutes. The animals were sacrificed at the end of the procedure.

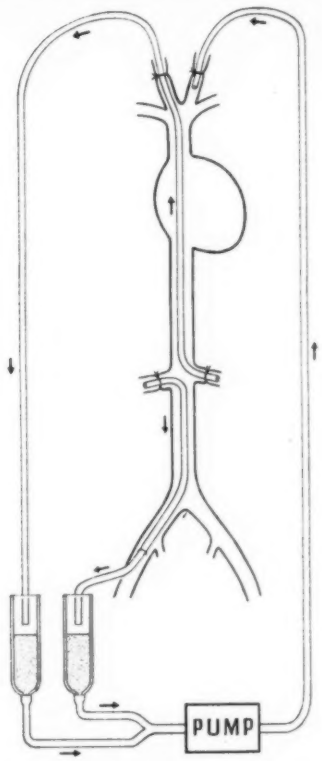

FIG. 1. Diagram illustrating method for measuring blood flow from each kidney.

There were 15 animals in this group, 8 with a right and 7 with a left thoracolumbar sympathectomy and splanchnicectomy. The blood flows were all measured when the animals had normal blood pressure. Blood was then withdrawn from a femoral artery until

TABLE I.—DATA CONCERNING RENAL BLOOD FLOW IN THE ANIMALS IN GROUP 1

State of kidney	Renal blood flow in c.c./kgm./min. Range	Mean	Renal blood flow in per cent of normal Range	Mean	No. of animals studied
Innervated	6.9–14.5	10.0	100	100	8
Denervated	8.4–19.9	12.4	102–140	124	8

the mean blood pressure was within the range of 60 to 80 millimeters of mercury. Studies of renal blood flow were then repeated. In 10 of the animals a more severe state of hemorrhagic shock was produced by the withdrawal of more blood until the blood pressure fell to a level of between 30 and 50 millimeters of mercury. In 8 of the animals in which severe shock was produced, blood was returned rapidly to the animal until the mean blood pressure became normal. Renal blood flow studies were then repeated.

Renal blood flow through the two kidneys was analyzed in two ways. First, the flow through each kidney was calculated in cubic centimeters per kilogram of body weight per minute. Secondly, the flow through the normally innervated kidney under normotensive circumstances was considered the normal renal blood flow and all other flows in that particular animal were considered as a per cent of this control value.

RESULTS

In all cases save 1 the denervated kidney had the greater blood flow when the animal had a blood pressure within the normotensive range. In all instances in which studies were carried out during moderate or severe hemorrhagic shock the denervated kidney had the greater flow. No appreciable difference was noted in flow values with regard to which kidney, right or left, had been denervated.

The results in the animals comprising group 1 are recorded in Table I. The renal blood flow of the normally innervated kidneys ranged from 6.9 to 14.5 cubic centimeters per kilogram per minute and averaged 10. The renal blood flow of the denervated kidneys ranged from 8.4 to 19.9 and averaged 12.4 cubic centimeter per kilogram per minute. The mean flow through the denervated kidneys was 24 per cent greater than that through the normally innervated kidneys.

The results in the animals comprising group 2 are recorded in Table II. The results of the initial studies under normotensive conditions were rather similar to those obtained in the animals in group 1. The renal blood flow of the normally innervated kidneys ranged from 4.3 to 16.6 cubic centimeters per kilogram per minute and averaged 9.6. The blood flow of the denervated kidneys was somewhat greater. It ranged from 6.5 to 18.3 and averaged 11.1 cubic centimeters per kilogram per minute. The mean flow of the denervated kidneys was 16 per cent greater than that through the normally innervated kidneys. When these same animals were subjected to moderate hemorrhagic shock the difference was increased. The innervated kidneys had flows ranging from 0.7 to 9.2 and averaged 3.9 cubic centimeters per kilogram per minute. The flows through the denervated kidneys varied from 2.7 to 12.6, and the mean was 6.8 cubic centimeters per kilogram per minute. When considered as per cent of the initial blood flow of the normal kidney under normotensive conditions the range of flow of the innervated kidneys was from 12 to 78 and the mean 41 per cent. The range of flow of the denervated kidneys was from 45 to 110 and the mean 71 per cent. The mean flow through the denervated kidneys was almost 75 per cent greater than that through the normal kidneys.

The 10 dogs subjected to a more severe degree of hemorrhagic shock showed a similar difference in renal blood flow of the two kidneys. The normal kidneys had flows varying between 0.1 and 5 and averaged 2.2 cubic centimeters per kilogram per minute. The denervated kidneys had flows ranging from 1.7 to 7 and averaged 4 cubic centimeters per kilogram per minute. The initial renal blood flow of the normal kidneys of these animals under normotensive conditions averaged 8.9 cubic centimeters per kilogram per minute. The mean flow of the

normal kidneys under shock conditions was 23 per cent of this value. That of the denervated kidneys was 87 per cent greater (43 per cent).

The renal blood flows of the two kidneys were more nearly the same after normal blood pressure was restored in 8 of these animals by retransfusion of the blood which had been withdrawn. The flows of the normal kidneys varied from 5 to 15 and averaged 10.2 cubic centimeter per kilogram per minute. The flows of the denervated kidneys ranged from 6.5 to 14.2 and averaged 10.9 cubic centimeters per kilogram per minute. The initial flows of the normal kidneys under normotensive conditions in these 8 animals averaged 11 cubic centimeters per kilogram per minute. The mean flows of the normal kidneys after retransfusion were 93 per cent of this value and those of the denervated kidneys 99 per cent.

TABLE II.—DATA CONCERNING RENAL BLOOD FLOW IN ANIMALS IN GROUP 2

State of kidney	Renal blood flow in c.c./kgm./min. Range	Mean	Renal blood flow in per cent of normal Range	Mean	No. of animals studied
INITIAL STUDIES UNDER NORMOTENSIVE CONDITIONS					
Innervated	4.3–16.6	9.6	100	100	15
Denervated	6.5–18.3	11.1	96–196	116	15
STUDIES DURING MODERATE SHOCK					
Innervated	0.7– 9.2	3.9	12–78	41	15
Denervated	2.7–12.6	6.8	45–110	71	15
STUDIES DURING SEVERE SHOCK					
Innervated	0.1–5	2.2	1.5–43	23	10
Denervated	1.7–7	4	19–60	43	10
STUDIES UNDER NORMOTENSIVE CONDITIONS AFTER RETRANSFUSION					
Innervated	5 –15	10.2	44–109	93	8
Denervated	6.5–14.2	10.9	70–118	99	8

DISCUSSION

One gains the impression from the data recorded in the literature that most investigators have found no evidence of any significant difference in blood flow through normal and denervated kidneys in unanesthetized animals or man. H. W. Smith believed that there was no evidence of renal denervation hyperemia and increased urine flow in the unanesthetized animal. Berne (2), using indirect methods, demonstrated no difference in blood flow through denervated and innervated kidneys of unanesthetized animals. Hiatt, who also used indirect methods, believed that denervation had no physiologic effect upon renal blood flow at normal and hyperemic levels. Those who have studied unanesthetized patients after sympathetic denervation for essential hypertension are in agreement that no significant effect of denervation upon renal blood flow was demonstrable.

Some workers, however, have observed differences in flow under the stress of anesthesia. Berne (2) found a 13 per cent greater plasma flow through the denervated kidneys of anesthetized animals. He thought that this difference was statistically significant. When Berne and Levy (3) studied renal blood flow by indirect methods in animals subjected to acute reduction of cardiac output, they observed no difference in flow through innervated and denervated kidneys, which they believed could not be ascribed to anesthesia. Selkurt believed that no appreciable difference in blood flow was evident through innervated and denervated kidneys other than that due to extraneous nervous influences when he studied by direct flow methods the renal blood flow of dogs subjected to gradually decreasing levels of aortic pressure. Rodrigues and Adriao demonstrated marked dilatation of renal capillary vessels as the result of both acute and chronic denervation. In man, Corcoran and his associates and Southworth found that caudal, spinal, and extradural anesthesia may bring about an increase in flow as measured by indirect methods.

Our experiments would tend to show that the denervated dog's kidney has somewhat greater blood flow than the normal under the stress of anesthesia. When the stress of hemorrhagic shock is added, this difference in flow is markedly increased. The mean flow of the denervated kidney of the dogs in severe hemorrhagic shock was nearly twice as great as that of the normal. Little difference in flow was noted after retransfusion. The latter observation may be dependent upon the inability of the denervated kidney

to undergo arteriolar dilatation, a phenomenon described by Spencer.

The fact that differences in renal flow in our experiments were in general more clear-cut than those observed by certain others may be related to two things. In the first place, our animals were subjected to complete unilateral sympathectomy and splanchnicectomy, while in most of the other animal experiments renal denervation was attempted by regional and probably inadequate sympathectomy, by stripping of the renal vessels, freeing of the renal pedicle, and by infiltration of the renal pedicle with anesthetic agents or alcohol. In the second place, we utilized a method of direct measurement of renal blood flow, while many who have inquired into this problem have used indirect methods. That indirect methods may not be entirely satisfactory under certain circumstances has been pointed out by Study and Shipley and by Kottke and Kubicek.

Our work would lead us to conclude that the normal dog under the stress of anesthesia and, more particularly, the stress of hemorrhagic shock has a greater blood flow through the denervated kidney than the normal one.

SUMMARY

By using direct methods for measuring differentially the renal blood flow of the two kidneys, greater flow was observed through the kidney denervated by previous extensive sympathectomy and splanchnicectomy. The difference was exaggerated when to the stress of anesthesia was added the stress of moderate or severe hemorrhagic shock.

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EDITORIALS

THE SELECTION OF A PROFESSOR

I. RIDGEWAY TRIMBLE, M.D., F.A.C.S., Baltimore, Maryland

A PLEA is made for broader consideration before selecting a person to fill a responsible teaching assignment, especially in the selection of those who are to head the various clinical departments of a medical school. The first criterion in the choice of a teacher in a college or a university is likely to be, as Charles G. Osgood of Princeton so well described, "not whether he has the humanistic passion, nor whether he has a Credo, but whether he is an expert in some narrow field, and is making it known to the world in print."

A narrow field, of course, implies specialization, and it is useless to blame or deplore specialization. It has of necessity come to stay; the fields of knowledge have become so many and so wide. However, specialization and true humanistic teaching are not incompatible, but one must bear in mind the further statement of Professor Osgood: "What must be remembered is that the human mind has no greater capacity for knowledge than it ever had. If it fills itself with highly specialized knowledge in a narrow field, it limits to that field its competence to judge or generalize, and that field contains but a very small holding in the wide realm of the whole truth. The actual effect—the deleterious effect upon the specialist—may be twofold. Either knowing right well how hard it is to gain a bit of exact knowledge even in a narrow field, the specialist modestly feels himself incompetent to judge in the larger fields of life and disclaims any authority or conviction in matters moral or spiritual. Or, as in certain known instances, the vanity of his expertness vaunteth itself; he believes that his recognized authority in one narrow compartment of knowledge qualifies him to utter judgment in the transcendent ranges of the human spirit. The very cocksureness of his unripe oracles often impresses, or depresses or perverts the immature undergraduate mind. In either case the true human balance is wanting."

It is of primary importance that the individual who is selected for the responsible teaching assignment be an expert in his chosen field or work. It is of equal importance that he not "scatter his shots" and divert his abilities into too many fields of endeavor.

He should, however, have demonstrated a willingness to participate in the prosaic as well as the esoteric. He must be ready to cope with problems dealing with closer relationships between the faculty and the ordinary physicians, with problems of the social aspects of medicine. He must not shun these responsibilities by withdrawing into his laboratory behind the safety of 17-ketosteroid estimations. He should have certain inherent qualities of "command," including a natural dignity, modesty, and quiet force. Of great advantage is an ability to meet people easily, to show a willingness to respect their ideas, to have a native cheerfulness or friendliness, and a sense of humor. Above all, anyone having so much control over the destinies of young people should have a magnanimity of spirit.

THE CAUSE OF DEATH IN ACUTE INTESTINAL OBSTRUCTION

JACOB FINE, M.D., F.A.C.S., Boston, Massachusetts

IN THE SIMPLEST FORM of acute obstruction of the small intestine fluids pour into the gut from the liver, pancreas, stomach, and enteric mucosa. These together with undigested solids, swallowed air, and locally generated gases rapidly raise the intraluminal tension, because the absorptive capacity of the mucosa proximal to the block is exceeded. The result is periumbilical colic, nausea, and vomiting. The effectiveness of the vomiting in reducing the pressure varies considerably, but it is seldom enough to prevent the persisting increase in pressure from impeding venous return. Consequently, the bowel wall at and above the site of obstruction becomes swollen and congested, with a resulting loss of fluid from the circulation into the lumen.

In the average case the first major development is a state of negative fluid and electrolyte balance. If the obstruction is correctly diagnosed and promptly dealt with by appropriate surgery, and by restoring fluid and electrolyte balance, there is a quick and successful end to the disorder. If perchance a closed loop obstruction is present but unrecognized, delay will prove disastrous because progressive interference with blood flow by the unrelieved and rising pressure within the loop will result in rapid devitalization, with perforation and peritonitis. But even in the usual case in which there is a proximal vent, the process going on in the loops immediately proximal to the block is equivalent to that produced by a tourniquet applied above normal venous pressure. Unless the intraluminal pressure is reduced to or below venous pressure by clearance of fluid and gas in these loops, the damage to the bowel wall will continue, and get worse. Tube suction often succeeds in lowering pressure, but it frequently fails to do so adequately, so that the congested bowel remains overdistended and eventually becomes atonic. Unless the obstruction is relieved, the patient's general state will deteriorate progressively. Even if perforation and peritonitis do not develop, such patients are prone to slip with apparent suddenness into profound shock.

When shock develops, and the question arises as to whether it is because of failure adequately to correct the fluid and electrolyte deficit, it is well to remember that a plasma loss also occurs in obstruction, and that the plasma deficit may be severe. If this loss has also been corrected, and fluid volume deficit is not the cause of the shock, then endotoxins from gram negative intestinal bacteria are likely to be the cause of the shock, even in the absence of an overt infectious process.

A good example of essentially the same type of toxic shock occurs in some patients shortly after reduction of a hernia containing strangulated bowel. In this situation a damaged loop of gut may be released and restored to the peritoneal cavity without resection because the surgeon judges the loop to be viable. The shock which develops soon thereafter may kill in the absence of significant fluid loss. The postmortem examination may disclose nothing more than a congested loop of bowel, with or without some hemorrhagic extravasation, and a small amount of serous or hemorrhagic transudate in the peritoneal cavity. In the experimental animal one can readily simulate what is going on in this patient simply by obstructing venous return from a loop of small bowel. This will cause fatal shock and death within 24 hours. The damaged

loop at death is heavy with blood and fluid. The loop may be necrotic and perforated. Even when it is not, the death is just about as rapid. Blood and fluid therapy do no significant good. But an effective antibiotic, whether put into the loop or the adjacent peritoneal cavity at the time of occluding the venous return, will prevent necrosis, shock, and death even if the blood and fluid lost into the loop are not replaced. Therefore, it is correct to ascribe the shock and death to bacterial activity at the site of impaired circulation.

Another related type of shock occurs when the superior mesenteric artery is occluded for some 30 to 60 minutes. Within an hour or two after release of the occlusion, the animal goes into deep shock and dies, in most instances, within a few hours. If the tissues are examined no gross pathology is seen except some swelling of the gut. Release of the ligature after 30 to 60 minutes is more rapidly fatal than if the ligature is not removed at all. This fact demonstrates that release of the ligature allows a lethal factor to flood the circulation. An antibiotic can prevent the shock and death. Therefore, the lethal shock-producing factor which enters the circulation must be of bacterial origin. The reason for the flooding is faster absorption of endotoxins owing to the vascular injury.

These experimental observations provide support for the need of prompt surgical intervention for mesenteric thrombosis or acute occlusion of the superior mesenteric artery. Many patients with these disorders die before the vascular injury has resulted in irreversible devitalization of the gut. The same is true of acute intestinal obstruction in which the vascular lesion is also the primary feature of the disorder. The threat of endotoxic shock should create a sense of urgency, and should lead to earlier intervention than is often practiced. Hence it is necessary to repeat what Leland McKittrick has been saying for so many years: "If the obstruction is of less than 24 hours' duration there is no room for delay of surgery." I believe the same is true for acute obstruction of more than 24 hours' duration. While the Miller-Abbott tube is a valuable adjunct to surgery, reliance upon it as the sole instrument in the hope that surgery may be avoided, or as the instrument of preference for obstruction of more than 24 hours' duration, can be disastrous. Reliance on the tube in acute obstruction of the small intestine is particularly treacherous.

The thesis that a bacterial factor is a major hazard in acute intestinal obstruction is not new. During the 1930's especially, this thesis received serious attention from numerous investigators. But it did not gain acceptance because of the disappointing results of the research then undertaken. Efforts to establish a significant role for the intestinal bacteria in most instances consisted of an experimental study of the consequences of intravenous injection of intestinal contents, or of extravasated peritoneal fluid, into healthy recipients. Either nothing happened, or death occurred without signposts as to the cause of death. Reliance on the response of healthy recipients to disclose the presence of a lethal toxin derived from the gut was in retrospect likely to fail, for the healthy animal has a substantial detoxifying potential, while the victim of obstruction may be progressively failing in this respect. Beginning with the work of Poth in the late 1940's, the evidence for the important role of bacteria came from the clearly protective effect achieved by sulfonamides and later by antibiotics. Even so, there is widespread resistance to the acceptance of a bacterial factor operating to produce death in acute intestinal obstruction, because it is generally held that bacterial toxins derived from the ordinary intestinal flora do not get into the circulation. Since bacteremia is a rare finding in obstruction, so the thinking goes, there is little disposition to believe that, in the absence of peritonitis, the shock preceding death can be due to bacterial action. Recently, however, evidence for the absorption of endo-

toxins from the gut has been receiving the attention of investigators. There is difficulty in getting such evidence because of the inadequacy of the techniques employed, especially for the detection of endotoxins in the blood or tissues. But evidence of recent date,[1] by utilizing immunologic techniques for identification of endotoxins of intestinal bacteria, indicates that endotoxins do get into the blood from the gut in both normal and disease states. The host's response to such toxins may be weak or absent if the general defense potential of the patient has been damaged. In that case, an endotoxemia may develop and cause a rapidly fatal collapse of the peripheral circulation.

More observations along these lines are needed to establish the claim for endotoxemia as a cause of fatal shock in acute intestinal obstruction. If this evidence is positive, the place for antibiotics as an adjuvant to surgery for obstruction becomes even stronger. But such therapy, like that for the fluid and electrolyte loss, cannot be considered more than secondary to surgery. The best protection against bacterial toxins is not antibiotic therapy but surgical treatment of the vascular lesion. By delaying surgery, the success of resection and anastomosis becomes increasingly doubtful. The fact is that some surgeons, like some internists and general practitioners, are sometimes dilatory in resorting to surgery because they are not sufficiently aware of the danger these patients are in, and having waited too long, they may lose the patient because of the general as well as the local deterioration that has occurred.

[1]This evidence is being obtained in my laboratory and will be published shortly.

THE SURGEON AT WORK

A LONG SUMP FOR OPERATIVE DECOMPRESSION OF OBSTRUCTED BOWEL

B. EISEMAN, M.D., F.A.C.S., T. EARLEY, M.D., T. BARTLEY, M.D., and FIELDS PAINTER, Denver, Colorado

AT THE TIME of laparotomy performed to relieve intestinal obstruction, it frequently is desirable to decompress the dilated bowel proximal to its point of obstruction. A 62 centimeter semirigid plastic sucker sump is described which has been employed at laparotomy to deflate the entire length of proximal small bowel.

The sump consists of an outer semirigid tube, 12 millimeters (¾ inch) in outside diameter, 6 millimeters (½ inch) in inside diameter, and 62 centimeters (24 inches) long (Fig. 1). It is made of teflon, a plastic that can be autoclaved, is sufficiently rigid to permit threading it into long segments of bowel and yet is sufficiently mobile and smooth so as not to perforate distended loops of gut. The distal end is perforated with 12 holes, 5 millimeters in diameter, spaced circumferentially throughout the terminal 14 centimeters of the tube. This outer sump is large enough to admit freely a No. 16 plastic Levin tube into its lumen.

At laparotomy a convenient point is chosen for insertion of the tube into the lumen of the distended bowel. If enterectomy is required, the long sump can be inserted through the open bowel. If not, the sump can be introduced through a purse-string suture, with the tip of the Levin tube placed immediately beneath the perforations. While constant suction is applied to the Levin tube, the long plastic perforated sump and its contained sucker is advanced into the distended bowel. If bowel contents clog the sucker, it can be removed and emptied while the plastic sump is left in place. As the bowel collapses, it is threaded on the long plastic sump in accordionlike pleats until the entire gut lies as though skewered on the sump (Fig. 2). Because of the length of the sump this procedure does not necessitate a great deal of manipulation of the

From the Department of Surgery, University of Colorado School of Medicine and Denver Veterans Administration Hospital, Denver.

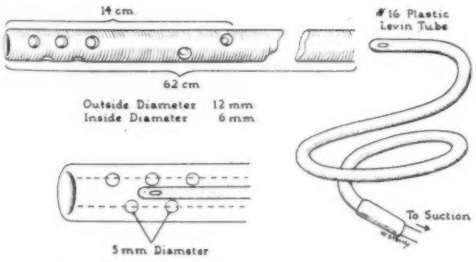

FIG. 1. Long plastic sump showing fenestrated tip.

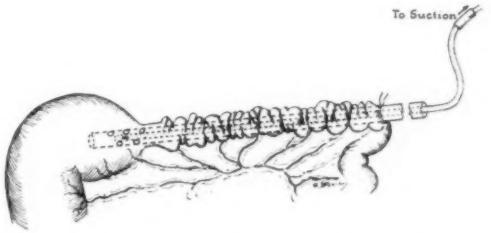

FIG. 2. Operative decompression of long segment of distended intestine utilizing sump with ensheathed Levin tube operating as a sucker.

bowel. When all of the bowel is decompressed, the sump is removed, the purse-string suture is tied, and the area is reinforced with 3 or 4 interrupted silk sutures.

Open decompression of distended loops of bowel at operation is a common technique but is usually only partially successful when performed with the ordinary short surgical sucker, as used by Barnes, or by needle aspiration, as advocated by Eske. Such decompression of the abdomen facilitates laparotomy closure, improves respiration, restores muscular tone to the bowel, and improves the blood supply of the distended gut. The technique which has been described has proved to be helpful in the operative decompression of such distended segments of bowel.

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THE USEFUL SPLENIC ARTERY

JOSEPHUS C. LUKE, M.D., F.R.C.S., F.A.C.S., Montreal, Canada

THE SPLENIC ARTERY is the only one in the body that can be employed as an effective autograft. This fact has been appreciated for many years and, prior to the use of homografts and plastic cloth arteries, the splenic had been used on a few occasions to replace arteries in distant locations. However, the added extensive operation necessary to obtain this autograft has militated against its value.

The usefulness of the splenic artery in replacing stenosed or aneurysmal vessels in the abdomen is described herein. This autogenous artery is to be preferred to all other types of grafts because of the decrease in immediate technical difficulties but particularly because of the absence of the late complications inherent in the use of small caliber homografts and plastic cloth grafts. Fortunately, an individual is not too greatly in need of a spleen and, consequently, sacrifice of this organ means but little. In preparing the splenic artery for an arterial shunt, the spleen can be removed, as was done in the first 2 cases, or the artery can be detached from the splenic pedicle and the organ otherwise be left intact. This latter procedure has been employed in the 4 subsequent cases. The isolated spleen apparently survives without its main blood supply, presumably because of adequate collateral circulation entering through the various ligamentous attachments. None of the patients with the isolated spleen showed any clinical or laboratory evidence of abdominal or hematopoietic derangements.

ANEURYSMS

The caliber of the splenic artery is too small to allow adequate replacement of the flow into the abdominal aorta. Its use in aortic aneurysms below the level of the renal arteries is unnecessary, as the technique of excision and grafting of these aneurysms has now become standardized. However, in the aortic aneurysm in which the origin of the renal arteries is also involved, the splenic artery can be advantageously used to revascularize one kidney before aortic excision and nephrectomy or anastomosis of the graft to the opposite kidney is carried out. In this technique at least one kidney is ensured of a good blood supply with only a short initial interruption.

From the Surgical Service, Royal Victoria Hospital, Montreal.

With increasing awareness and particularly with the widespread use of aortography, more and more aneurysms of the major branches of the abdominal aorta are being discovered. For instance, one third of all reported renal artery aneurysms have appeared since 1951, according to Glazer and Lombardo. Poutasse described 12 cases, 6 of which showed the typical signet ring appearance on the plain roentgenogram. Nesbit and Coenshaw believe that only 25 per cent of renal artery aneurysms show this signet ring calcification. Harrow and Sloane have collected 180 cases of all types of renal artery aneurysms and state that there is no definite history of rupture of the calcific type. They report 24 cases in which rupture of the noncalcific type occurred with 20 deaths.

Renal artery aneurysms are almost invariably treated by nephrectomy, but it is much more ideal to preserve this relatively normal kidney by excision of the aneurysm and restoration of normal flow with a splenic artery shunt. The only contraindication to this renal preservation is the presence of the aneurysm in the renal pedicle, allowing no adequate distal artery for the shunt attachment.

Common hepatic artery aneurysms are somewhat less common, but Hansbrough and Lipin have collected a series of 111 cases. Twelve of these patients have been treated surgically but none until the case that follows had been managed with a splenic artery shunt and excision of the aneurysm. The methods employed in the previously described cases have included ligation, wiring, endoaneurysmorrhaphy, excision, and cellophane wrapping. Ligation and excision are logical if the aneurysm is proximal to and not interfering with the gastroduodenal branch, as this artery is adequate, through retrograde flow by way of the collateral channels about the pancreatic head, to extend sufficient

blood into the distal hepatic artery to arterialize the liver. However, hepatic artery aneurysms are usually fusiform, and it is rare that the gastroduodenal branch will be spared. Total interruption of the hepatic artery with reliance upon the other collaterals is begging for liver necrosis.

CASE 1. A male, aged 59 years, was admitted to the Royal Victoria Hospital on 10 March 1959 with a 5 year history of epigastric distress and episodes suggestive of biliary colic. A nonfunctioning gallbladder was found by roentgenography. The patient's blood pressure was 180/105 millimeters of mercury and his blood cholesterol level was 191. Cholecystectomy and appendectomy were performed for a chronically inflamed gallbladder containing stones. At this operation an aneurysm of the common hepatic artery measuring 6 by 8 by 4 centimeters was discovered. Reoperation was carried out on 25 March when the aneurysm was explored further and found to arise 2 centimeters from the aortic origin of the common hepatic artery. The right gastric and gastroduodenal arteries arose from the aneurysm which showed marked bulging and thinness of its ventral wall. The pulsation of the distal stub of the hepatic artery was feeble. The splenic artery was mobilized from the spleen, leaving the latter intact. Dissection of this artery was carried medially to the aorta, and the left gastroepiploic and pancreatic branches were ligated. The splenic artery was then swung to the right and anastomosed end-to-end to the distal stub of the hepatic artery about 2.5 centimeters from the hilus of the liver. A small but total area of thrombus had to be removed from the distal hepatic artery before anastomosis. The aneurysm was excised after proximal ligation of the hepatic artery close to the aorta. Good pulsation of the shunt and distal hepatic artery was observed. The patient's convalescence was uneventful. No change in liver function tests occurred subsequent to this second operation. The postoperative cholesterol level was 161.

Aneurysms close to the origin of the superior mesenteric artery can be dealt with in exactly the same manner as was the common hepatic aneurysm just discussed. Any of these aneurysms, if technical difficulties exist in their excision, can be left in situ after proximal and distal ligation and splenic artery bypass. Splenic artery aneurysms need not enter into this discussion, as ligation with or without excision is adequate treatment.

OCCLUSIVE ARTERIAL DISEASE

Acute superior mesenteric artery occlusion usually occurs as the result of atherosclerotic disease and, rarely, embolism involving the first inch of this artery. If thrombosis distal to the initial occlusion occurs, gangrene of the bowel develops rapidly, and intestinal resection is required. Various isolated reports have appeared in which the initial occlusion has been successfully removed by embolectomy or thromboendarterectomy and followed by restoration of intestinal circulation. It is suggested that bypass of this occluded area by employing the splenic artery would be safer and simpler. The anastomosis to the mesenteric artery can be performed with greater ease below the inferior border of the pancreas.

The condition in which splenic artery shunt will find its greatest use is in stenotic lesions of the renal artery that give rise to arterial hypertension. Many varieties of renal artery stenosis exist, mainly intrinsic but occasionally extrinsic. Atherosclerotic plaques are far and away the greatest single cause. Because of improved methods of investigation, more and more cases of Goldblatt kidney are being discovered and, rather than nephrectomy of this relatively normal kidney, many of them can be revascularized by employing the splenic artery with consequent relief of the hypertension. Particularly is this indicated if there is any evidence of bilateral renal artery stenosis, in which case one kidney can be removed and the other revascularized.

In the past year our "renal team" has investigated 18 cases in which renal artery stenosis was a possible cause of hypertension. Eight patients were found to meet the criteria and were treated surgically. Three patients required nephrectomy because the arterial lesions were too adjacent to the kidney pedicle for revascularization to be feasible. Five patients were treated by revascularization employing the detached splenic artery.

There are three diagnostic tests upon which most reliance is placed in establishing a diagnosis of renal artery stenosis. Brust and Ferris described the response of the blood pressure to an intravenous dose of 400 milligrams of tetraethylammonium chloride in cases of renal artery stenosis. A stable or slight rise in the blood pressure in the subsequent 20 minutes is a positive response. In other types of arterial hypertension, a marked fall occurs. This test is given on an outpatient basis and, if response is positive, the patient is admitted for further investigation. Renal excretion tests with catheters in each ureter are carried out by the urologist. These studies must be most carefully made to be of value. In the patient on a previous diet high in sodium, the

excretion studies are positive by the Howard test if one kidney reveals a 15 per cent or more decrease in sodium excretion and a 50 per cent drop in water output in comparison to the opposite kidney. Aortography is then performed to give direct visualization of the renal arteries. Originally, aortography was performed by the usual translumbar needle technique but has recently been changed to the Seldinger method. This latter technique consists of introducing a special catheter percutaneously into the femoral artery and directing it cephalad to just above the renal arteries. The catheter tip allows spraying of the contrast medium in all directions into the aortic stream and, with this proper diffusion, a more complete flow into both renal arteries is possible. The former translumbar needle technique gave inconstant renal artery filling since the medium was poorly mixed with the aortic blood because of the single opening and single direction of the needle tip.

OPERATIVE TECHNIQUE

The operative approach to the spleen, if the best possible exposure is desired, is through a thoracoabdominal incision at the eighth or ninth interspace with the patient in a 45 degree lateral position. The incision is extended into the abdomen, ending below and to the left of the umbilicus. The spleen is fully visualized and the splenic artery can be easily identified and detached just proximal to its division into the various splenic hilar branches. In the dissection of the splenic artery proximally toward the aorta, the left gastroepiploic artery is encountered and various small pancreatic branches require ligation. If the splenic artery is to be transplanted into the left renal artery this exposure is adequate (Fig. 1). The kidney is exposed by shifting the splenic flexure and descending colon medially. The renal vessels are readily cleaned and the renal artery lesion is confirmed by the presence of a poststenotic dilatation, a thrill, and palpation of the offending lesion.

When the splenic artery is to be swung to the right of the midline, simultaneous exposure of the spleen and the right sided lesion becomes more difficult. A complete transverse incision just below the costal margin with an upward curve toward the xiphoid process gives adequate exposure of the entire upper part of the abdomen. In lesions on the right side the splenic artery must be dissected completely to its aortic

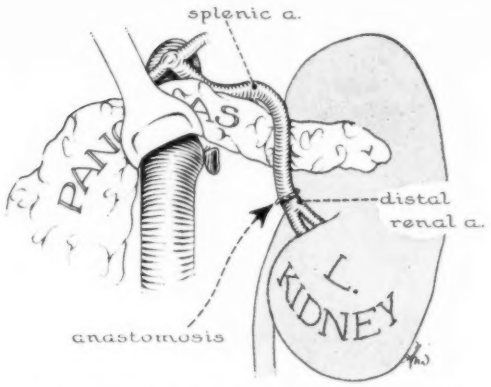

FIG. 1. Cases 2 and 3. End-to-end splenic to renal arterial anastomosis after excision of the diseased portion of the renal artery.

origin to give adequate length. To reach the right renal artery, a tunnel is constructed ventral to the inferior vena cava, passing dorsal to the head of the pancreas to emerge at the upper border of its neck. In this area, the firm tissue of the celiac ganglion must be penetrated so as to draw the splenic artery into the tunnel. In this manner, the length of the splenic artery will be quite adequate to reach the right renal artery without tension. When the superior mesenteric or common hepatic arteries are to be replaced, this tunnelling is unnecessary.

The anastomosis performed can be either end-to-end or end-to-side. In aneurysm replacement the anastomosis is preferably end-to-end after excision of the aneurysm. When the splenic, hepatic, or renal arteries are clamped and cut, their caliber decreases to a relatively small size and end-to-end anastomosis should be performed with the vessels cut on the bias to allow as wide a lumen as possible. In renal artery stenosis, if there is a relatively good flow in the narrowed renal artery, the preferred technique is to utilize an end-to-side splenic to renal arterial anastomosis (Fig. 3) distal to the obstruction, thereby greatly augmenting the existing flow. This end-to-side anastomosis is frequently facilitated by the existence of an area of poststenotic dilatation in the renal artery.

CASE 2. A male, aged 51 years, was admitted to the Royal Victoria Hospital complaining of dizziness, headache, and blurred vision. It was known that he had been hypertensive for 12 years, and he had been admitted twice previously for investigation of this

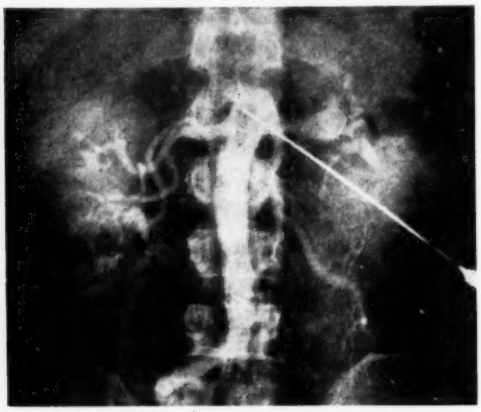

FIG. 2. Case 5. Percutaneous aortogram revealing stenosis of the left renal artery with poststenotic dilatation.

condition. His blood pressure in the hospital ranged from 170/100 to 220/130 millimeters of mercury and response to antihypertensive drugs was poor. The urine was normal, although the patient had had two attacks of painless hematuria in the weeks preceding admission. The nonprotein nitrogen was 24 and the 17-ketosteroids were normal, but the corticoids were elevated. The intravenous pyelogram reading was normal, and differential excretion studies showed decreased phenolsulfonphthalein excretion from the left kidney. On the other hand, the creatinine clearance was better on the left than on the right. The etamon test showed a rise in blood pressure over a 10 minute period. An aortogram showed a poststenotic dilatation in the left renal artery.

The spleen and kidney were approached by a thoracoabdominal incision on 3 June, and a hard arteriosclerotic plaque was found in the left renal artery three-quarters of an inch from the aorta. A well marked poststenotic dilatation was present with a thrill. The spleen was removed and the splenic artery was dissected free. Arteriosclerotic plaques were also found in this artery which had to be cut back until a proper sized lumen was obtained. The involved section of the renal artery was removed and an end-to-end splenic to distal renal arterial anastomosis performed. The renal blood flow was interrupted for 17 minutes.

Postoperatively the patient had an immediate improvement in vision and also relief of his former symptoms. The blood pressure varied from 160/100 to 120/80 millimeters of mercury. After discharge it rose to 180/110 millimeters of mercury, but now responds well to small doses of antihypertensive drugs and the patient is symptom-free.

CASE 3. A male, aged 55 years, was admitted to the Royal Victoria Hospital on 8 July 1958 complaining of symptoms suggestive of disc disease with sciatic pain. The blood pressure was 230/160 millimeters of mercury. The urine showed a moderate number of hyaline casts and the blood nonprotein nitrogen was 26. The patient had grade 3 hypertensive retinopathy on the right and grade 2 on the left. The Howard test showed marked decrease in water and sodium excretion from the left kidney. The creatinine clearance and phenolsulfonphthalein excretion were also decreased on the left. The etamon test showed an initial drop but rose well above the preinjection level in the latter part of the test. A lumbar aortogram revealed a well marked poststenotic dilatation in the left renal artery. Operation was performed on 10 July 1958, again through a thoracoabdominal incision. Splenectomy, resection of the involved renal artery, and end-to-end splenic to renal arterial anastomosis were performed. Postoperatively the patient's blood pressure varied from 118/70 to 140/100 millimeters of mercury.

He was readmitted for assessment on 1 October 1958 with a blood pressure reading of 145/85 millimeters of mercury. The nonprotein nitrogen was 21, the intravenous pyelogram was normal, and differential excretion studies were now all normal for sodium, water, and phenolsulfonphthalein. It was noted that there was a marked improvement in the patient's fundi.

CASE 4. A male, aged 47 years, was admitted to the Royal Victoria Hospital on 7 October 1958. He was discovered to have had hypertension 13 years previously but had no related symptoms. The urine showed a trace of albumin and occasional hyaline and granular casts. The blood pressure varied in the hospital from 140/90 to 200/110 millimeters of mercury. Excretion studies showed decreased phenolsulfonphthalein from the left kidney and decreased water and sodium excretion in comparison to the right kidney. The etamon test produced a drop in systolic pressure but a slight rise in the diastolic. On the basis of findings from this test the patient did not fit into the group with renal artery stenosis. Aortography was performed on 3 occasions and each time showed decreased filling of the left renal artery in comparison to the right. The nephrogram showed less density and more delay in function on the left than the right. No definite stenosis of the left renal artery could be seen but the aortorenal junction was not clearly visualized. No poststenotic dilatation was seen. On the basis of the differential excretion studies plus the suggestive arteriogram, operation was performed on 23 October through a thoracoabdominal incision. The splenic and renal arteries were smaller than normal and went into intense spasm when handled. Despite a thrill in the renal artery no areas of stenosis could be demonstrated to the aortic junction. The splenic artery was detached from the spleen, leaving the latter in situ, and was anastomosed end-to-side to the distal renal artery just proximal to its bifurcation.

Postoperatively the blood pressure varied from 110/70 to 190/100 millimeters of mercury and, since the patient's discharge, has remained slightly lower than in the preoperative state.

CASE 5. A male, aged 36 years, was admitted to the Royal Victoria Hospital on 15 October 1958 complaining of headache, pounding in the chest, and buzzing in the right ear for the past 3 months. The blood pressure was 220/140 millimeters of mercury. The intravenous pyelogram was normal and showed

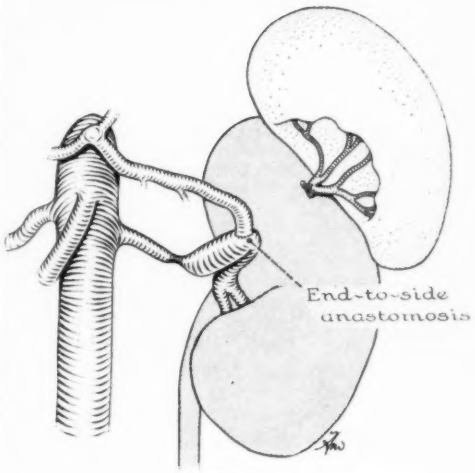

FIG. 3.

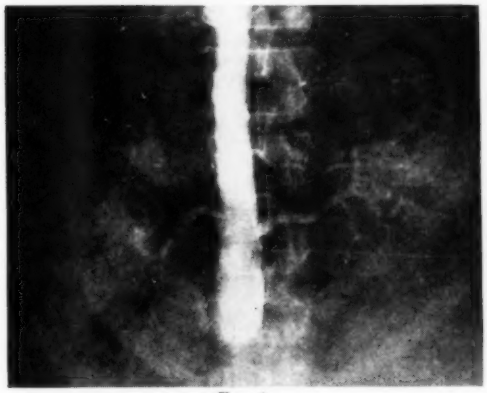

FIG. 4.

FIG. 3. Cases 4, 5, and 6. End-to-side splenic to renal arterial anastomosis augmenting the flow in the stenosed renal artery.

FIG. 4. Case 6. Seldinger aortographic technique showing right renal artery stenosis at the aortic origin.

equal sized kidney shadows. The fundi were grade 2. An aortogram revealed a very large poststenotic dilatation involving the left renal artery (Fig. 2) sufficiently large to resemble an aneurysm. With this positive finding, differential excretion studies and the etamon test did not appear necessary, and operation was performed on 20 October 1958. Through a left thoracoabdominal incision the splenic artery was detached from the spleen and brought down and anastomosed end-to-side to the very large poststenotic dilatation in the left renal artery (Fig. 3). This dilated portion occupied over half the length of the renal artery and extended up to the point of its bifurcation, making an end-to-end splenic to renal arterial anastomosis impossible. A hard plaque was present in the renal artery about 2 centimeters from its origin and a marked thrill was present in the poststenotic portion.

Postoperatively the patient's symptoms immediately disappeared and his blood pressure progressively lowered from 160/104 millimeters of mercury on the first day to 124/80 on the sixth. He has been symptom-free and normotensive since.

CASE 6. A female, aged 40 years, was admitted to the Royal Victoria Hospital on 17 January 1959. She had been aware of hypertension since the age of 18, with blood pressure ranging from 200/120 to 240/140 millimeters of mercury. She had sought advice at various centers in the past and had been labelled as an essential hypertensive. In May 1957 she suffered from a mild stroke from which she recovered and in April 1958 had an attack of congestive heart failure. Her present complaints consisted of throbbing headache, blurring of vision, and episodes of nausea and vomiting.

Investigations revealed normal nonprotein nitrogen and blood sugar levels. Cholesterol reading was 211. No abnormal findings were present in the urine. The electrocardiogram was normal and the fundi revealed grade 2 changes. The etamon test revealed no fall in blood pressure in 20 minutes. The Howard test showed a marked decrease in sodium, water, creatinine clearance, and phenolsulfonphthalein excretion from the right kidney in comparison to the left. Aortography carried out by the Seldinger technique showed both renal arteries to be smaller in caliber than usual but with definite stenosis at the aortic origin of the right (Fig. 4).

Operation was carried out on 3 February through a long transverse incision. Detachment of the splenic artery from the spleen and its transference to the right, according to the technique previously mentioned, were performed. An end-to-side anastomosis was carried out with the right renal artery in its portion extending to the right of the vena cava. The patient was discharged on 15 February with a blood pressure reading of 150/90 millimeters of mercury. Since the patient's return home, the headaches have disappeared, her vision has improved, and she reports herself as feeling much improved.

SUMMARY AND CONCLUSIONS

1. The splenic artery is an ideal autograft for use in replacing other major abdominal aortic branches at the site of occlusive arterial disease or aneurysm formation. The splenic artery can be obtained by splenectomy or, preferably, by detaching it from the splenic pedicle without splenectomy.

2. When dissected to its aortic origin, the splenic artery can be swung to the right to replace the common hepatic or right renal arteries. The superior mesenteric and left renal arteries are readily reached. End-to-end or end-to-side anastomosis can be performed by either

excising or bypassing the particular lesion concerned.

3. Six cases are described in which this technique was employed, in 1 to replace an aneurysm of the common hepatic artery and in 5 to revascularize the kidney in cases of arterial hypertension, the result of the Goldblatt mechanism. In 4 the procedure was carried out on the left side and in 1 on the right.

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TECHNIQUE OF SPHINCTEROPLASTY IN RECURRENT PANCREATITIS

GEORGE L. NARDI, M.D., F.A.C.S., Boston, Massachusetts

DIVISION of the sphincter of Oddi is a currently accepted procedure in the surgical management of recurrent pancreatitis. The technique of the procedure is, however, far from standardized, and this lack may account for some therapeutic failures.

The procedure has for its objective the permanent relief of any obstruction, organic or spastic, to the outflow of pancreatic secretions. A simple ½ centimeter slit of the ampulla may, on occasion, provide the desired result but frequently will not relieve any obstruction and may even restenose, according to Brown and coworkers.

Jones and associates have stressed the importance of performing a sphincteroplasty rather than a sphincterotomy, with complete unroofing of the intraduodenal portion of the common duct and a careful mucosa to mucosa suture of choledochal and duodenal epithelium. The desirability of carrying out such a complete sphincteroplasty is well supported by the anatomic studies of Boyden. Incomplete division of the muscles proximal to the papilla by a simple limited sphincterotomy may leave many muscle bundles intact to continue an obstructive role on both biliary and pancreatic ducts, regardless of whether a common channel, the ampulla of Vater, is present or not. In order to guarantee proper biliary and pancreatic drainage, a complete section of this muscle should be carried out, that is, a sphincteroplasty.

Performance of this more extensive procedure is not without hazard, since the longer incision in the intramural portion of the common bile duct can easily result in duodenal perforation into the lesser omental sac. To obviate this hazard it is of the utmost importance to secure a

From the Department of Surgery of the Harvard Medical School at the Massachusetts General Hospital, Boston.

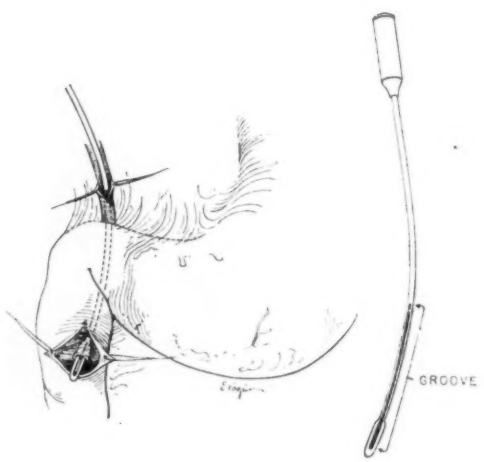

FIG. 1.

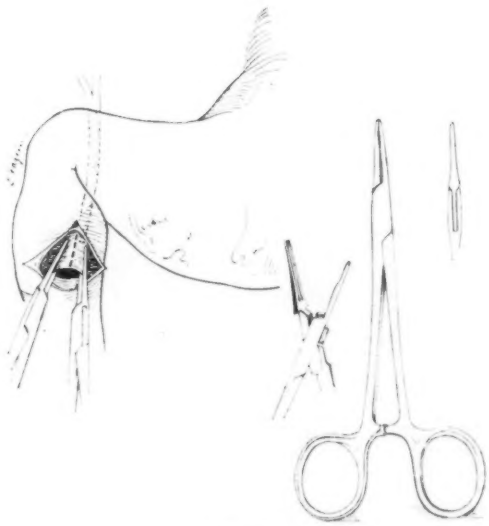

FIG. 2.

FIG. 1. The grooved dilator in use.
FIG. 2. The honed and serrated forceps in use.

careful and thorough approximation of biliary and duodenal mucosa, particularly at the apex of the incision.

The technique utilized is a combination of the sphincteroplasty of Jones and associates plus the additional pancreatic duct exploration advocated by Bartlett and McDermott. By grooving the terminal portion and olive of a set of Bake's dilators there is readily available an instrument upon which a knife blade or the blade of a pair of scissors can be inserted as a guide for the safe and accurate division of the sphincter muscle (Fig. 1).

Once the initial incision is made, specially designed mosquito forceps whose blades have been honed down laterally and with the jaw serrations grooved longitudinally (Fig. 2) can be inserted easily and safely into the common duct and division carried further in steps. Sutures of No. 5–0 chromic catgut are then inserted around the jaws of the snaps before their removal, thus guaranteeing accurate mucosal approximation and insuring against a potentially disastrous leak.

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Reviews of New Books

THE VERY SUCCINCT REPORT *Cancer in Families*[1] deals with the occurrence of cancer within family groups, i.e., the distribution of the disease among relatives of a person who has cancer as compared to its incidence among relatives of a person who does not have cancer. While the frequency of cancer in families has been studied by a number of other observers, the variations in conclusions from such efforts stimulated these authors to conduct a double survey. The original study was planned to determine whether or not cancer of the breast occurred with unusual frequency among the female relatives of a woman in whom the disease had developed in this site. The frequency of cancer in sites other than the breast was also determined. After this information had been collected, the authors decided that the occurrence of the disease in the male relative should be studied, thereby shifting the emphasis from breast cancer to cancer in all sites.

The study population was composed of two groups of families, one in which a living white proband had cancer of the breast, and the other in which a living proband did not have cancer. Two generations were interrogated, that of the probands and that of the parents of the probands. Experienced field workers interviewed 200 probands and also as many of their relatives in each generation as possible. The information which was obtained from these individuals was augmented by information from physicians, hospitals, bureaus of vital statistics, undertakers, and officials of cemeteries in the area around the city of Philadelphia.

Despite the fact that there are an admittedly large number of difficulties involved in securing accurate information upon the familial aggregation of a disease, the reported data appear to be valid as the study population was investigated twice. On the second survey, the roster of names of females was checked and names previously omitted plus the male members of the families were added. This gave opportunity to measure the completeness of reporting females in the first survey. The cancer probands were white women, between the ages of 40 and 65, who had been admitted to any of 28 hospitals in Philadelphia and surrounding towns for treatment of cancer of the breast during the 5 years immediately prior to the start of the study. The control probands were living white women who were between the ages of 40 and 65 whose names were taken from the files of the Institute's School of Dentistry of the University of Pennsylvania. They were individuals who were admitted to the clinic during the same years in which the cancer probands had applied for hospital treatment. In no case did a control proband report having had cancer.

The study revealed no statistical differences between the relatives of the cancer and control probands with respect to the frequency of cancer in any specific site including the breast; in the same site in mother and daughter, in all sites; in either generation; in the number of cases of cancer in the family group; in daughters of cancerous and noncancerous mothers; and in sons of cancerous and noncancerous fathers. The authors concluded that if a familial tendency to develop cancer did exist, it was not large enough to be detected in a study of this size.

The data reported in this work have been scrutinized as closely as possible in order to detect any bias which might have made its way into the report. It was concluded that the control and study populations were such that any differences which might be found between them would be real differences, and not the result of any bias in either the selection of the controls or the collection of the information. In those instances in which there was a statistically significant difference between the cancer and control groups with respect to the frequency of cancer, it was found in the more remote rather than in the closer relationships to the proband, and the higher frequencies of the disease appeared in the control rather than in the cancer groups. Such findings do not constitute evidence of any familial tendencies. The best explanation is that they were occasional chance differences which the significance test criteria label as statistically significant.

There is little question but that this is a very objective report and should be read by all clinicians and investigators who express an interest in this problem. Certainly for those who have a "subjective feeling" with regard to the hereditary aspects of malignant disease, the objectivity of this report should facilitate the clarification of unsubstantiated conclusions.

—*Walter W. Carroll.*

[1]CANCER IN FAMILIES; A STUDY OF THE RELATIVES OF 200 BREAST CANCER PROBANDS. By Douglas P. Murphy, M.D., and Helen Abbey, Sc.D. 76 pages. $2.50. Cambridge, Mass.: Published for the Commonwealth Fund by Harvard University Press, 1959.

THE BOOK *Basic Surgery*[2] has been written almost entirely by a small group of surgeons in London, each an authority in his field. The editor is a neurosurgeon. It is an unusual textbook for undergraduate students because the usual chapters on pathology and the other basic sciences in their relation to surgery have been omitted. The individual sections vary somewhat in style and degree of excellence, but, generally, each subject is covered thoroughly. More operative surgery has been included, perhaps, than the undergraduate student need know.

This is an excellent work of reference for one at any level in the profession, but in spite of the editor's statement that it has been written primarily for undergraduates it would seem more suitable for graduate students and residents, including those preparing for the higher examinations. —*Robert M. Janes.*

IN THE SECOND EDITION of the authoritative text *An Atlas of Normal Radiographic Anatomy*,[3] the author has made many improvements. Several techniques are described for measuring deviations from normal skeletal anatomy, and this continues to be an outstanding feature. The chapter on growth and development is particularly well done and includes a great deal of useful information relating to the pelvis and dislocated hips in children. The anatomy of the brain is beautifully demonstrated by ventriculographic and arteriographic methods. The author, an expert in the field of anatomy of the spine, has thoroughly covered this subject in a manner which will be very helpful to all physicians dealing with problems of the back. There are also new sections dealing with angiocardiographic and angiographic demonstrations of the anatomy of the circulatory system. The sections on bronchographic and gastrointestinal anatomy are characteristically complete and accurate.

There are so many outstanding features in this book that it is difficult to find points for adverse criticism. The section dealing with x-ray protection is necessarily brief, and one wonders whether it is wise to attempt to cover such a subject, albeit an important one, in a book on anatomy. Some of the illustrations would have been improved if the quality of the roentgenograms had been better and if they had not been reproduced by the Log-etronic method. No mention is made of the retrograde aortographic studies of the anatomy of the aortic valve regions and coronary arterial circulation.

The excellent features of this book make it a "must" for anatomy teachers, roentgenologists, and other physicians who have to deal with anatomy as depicted in roentgenograms. The scope of the anatomic material included will make this a daily reference in radiology departments in which residents are being trained. The book will also be of great value to all physicians who must have knowledge of the roentgenographic anatomy for use in diagnosis.

—*Sidney W. Nelson.*

THE FIRST EDITION of the book *Roentgendiagnostik des Magen-Darmkanals*[4] by R. Prévôt and M. A. Lassrich comprises much of the work previously published under the title *Grundriss Roentgenologie des Magen-Darmkanals*. This book is intended primarily for those interested in gastroenterology but should not fail to attract the attention of surgeons and internists alike.

The book clearly describes the technique of roentgenologic examination of the gastrointestinal tract and compares the various opaque media generally employed. The esophagus, stomach, duodenum, small intestine, and gallbladder are all covered in individual chapters and in many instances the clinical findings are detailed and a photograph of the appropriate surgical specimen is included. Obviously, in a book of this nature, the quality of the illustrations is of prime importance and in this respect the work certainly excels. Every conceivable disease of the gastrointestinal tract is depicted and many of the excellent plates illustrate the varying roentgenographic appearances of different disease processes while others show some of the more uncommon lesions, such as tuberculosis of the colon. One such plate demonstrates simultaneously a tumor of the stomach and hepatic and splenic flexures of the colon. Pediatric problems are not omitted and are well covered.

There is much in this book to interest the diagnostician and a great deal can be learned without a profound knowledge of the German language.

—*Ronald H. Hayward.*

AS IN YEARS PAST, the excellent volume of *Collected Papers of the Mayo Clinic and the Mayo Foundation*[5] contains a comprehensive selection which should be of interest to the general practitioner as well as the specialist. The first 12 papers are devoted to heart surgery and extracorporeal circulation. The outstanding achievements which are recorded exemplify the emphasis that has been placed on research by the Mayo Clinic, and serve to point out the results obtained with a comprehensive research program.

In the section on the alimentary tract, reflux esophagitis and its correction by the operation devised by Ellis would appear, at present, to be a worthy contribution. The controversial subject of pancreatitis is covered in some detail, and although one may not agree with the conclusions relative to the pathologic mechanisms, there is a wealth of stimulating material in this section. The review of carcinoma in situ of the cervix in the chapter on genitourinary disease is remarkable. Another topic which should be of interest is the review of the significance and treatment of the

[2]BASIC SURGERY. Edited by Leslie Oliver, M.B., B.S. (Lond.), F.R.C.S. (Eng.), F.A.C.S. 1359 pages, 680 illustrations including 4 color plates. $26.50. Springfield, Ill.: Charles C Thomas, 1959.

[3]AN ATLAS OF NORMAL RADIOGRAPHIC ANATOMY. By Isadore Meschan, M.A., M.D. Assisted by R. M. F. Farrer-Meschan, M.B., B.S. (Melbourne, Australia), M.D. 2nd ed. 759 pages, 1466 illustrations. $16.00. Philadelphia and London: W. B. Saunders Co., 1959.

[4]ROENTGENDIAGNOSTIK DES MAGEN-DARMKANALS. By Prof. Dr. R. Prévôt and Priv.-Doz. Dr. M. A. Lassrich. 346 pages, 544 illustrations. $18.30. Stuttgart: Georg Thieme Verlag, 1959.

[5]COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Editorial Staff: Carl M. Gambill, A.B., M.D., M.P.H., James R. Eckman, A.B., M.A., Ph.D., M. Katharine Smith, B.A., Florence L. Schmidt, B.S.E., George G. Stilwell, A.B., M.D., and Guy Whitehead, B.A., M.A., Ph.D. Compiled by George G. Stilwell, A.B., M.D. Vol. 50—1958. 791 pages, illustrated. $13.00. Philadelphia and London: W. B. Saunders Co., 1959.

prostatic nodule, which clearly points out the pitfalls in arriving at a clinical diagnosis based simply upon the degree of induration of a prostatic nodule palpated at rectal examination.

The section on Ductless Glands reflects the changing therapy of disorders of the thyroid gland, as well as other endocrine abnormalities. The rationale of performing only a lobectomy for papillary carcinoma of the thyroid gland in the absence of nodal metastases is supported by extensive experience. The paper on Primary Hypo-Parathyroidism by Randall and King should stimulate recognition of this disease when the usual clinical manifestations are entirely lacking.

The surgeon as well as the hematologist will find a great deal of interest in the section on Blood and Circulatory Organs. Particularly interesting is the Surgical Aspects of Hypersplenism by Ferris. Surgical Therapy of Occlusive Peripheral Atherosclerosis by Estes paints a rather pessimistic view of the long term results of therapy in this field. This pessimistic view does not parallel the experience in other centers in which brilliant original contributions have been reported in the management of occlusive disease. Estes' report is based upon 250 grafts, with 70 to 80 per cent successful results. Homografts apparently were being used at the time of publication of this paper. Homografts have since been abandoned in favor of synthetic prostheses, as well as endarterectomy, by practically all surgeons in this field. With these latter methods, good, long term results have been reported.

In the section on the Head, Trunk, and Extremities, the work on cosmetic correction of severe mandibular retrusion is excellent.

Several interesting topics are discussed in the section on the Thorax, including the ruptured diaphragm, pulmonary infarctions, and disseminated indeterminate pulmonary disease. Pulmonary Resection of Mineral Oil Granulomas is of special surgical interest, as is the report on Pulmonary Resection for Metastatic Tumor. This latter paper should encourage the removal of metastatic tumors in patients who would otherwise be doomed. The subject of Physiologic Considerations and the Diagnosis and Treatment of Ventilatory Insufficiency is concise and interesting.

The report of Management of Acute Injuries of the Head contains many practical points which may be life-saving if utilized by any general surgeon. All surgeons should be familiar with the points stressed relative to the management of head injuries, especially in children.

This volume is as valuable as the "*Collected Papers*" of the past. The illustrations and arrangement of subject matter are superior and clearly show the wisdom of having an editorial section devoted solely to the organizing and gathering of material for publication.

—*Lucius D. Hill.*

BASED MAINLY UPON his own experience, Grewe gives in a short, clear, and precise form directions for handling surgical emergencies in the newborn, infants, and children.[6] He covers general surgical, urologic, and orthopedic procedures, emphasizing the practical aspects in management rather than theoretic considerations.

In part A, the newborn period is discussed and its surgical conditions subdivided according to body regions, such as the head, neck, and chest. Part B is concerned with infancy and childhood. Emphasis is put on differential diagnosis and indications or contraindications for surgery varying with age and other factors. For each surgical condition pertinent data are presented as to age incidence, important symptoms and signs, and diagnostic aids for confirmation or exclusion. A short plan for management is usually outlined, considering preoperative measures, the type of surgical procedure, and postoperative care. Directions are given regarding the use of antibiotics, fluid restoration, nourishment, the type of anesthesia, and its practical application in each condition. The technique of the surgical procedure is described indicating the preferable site of the skin incision and enumerating the sequence of operative steps. Often one or more alternatives are given for situations when the surgeon finds himself confronted with an unexpected pathologic condition during surgery. Valuable practical points are brought out in respect to peculiarities in childhood and infant surgery.

In a separate chapter anesthesia in general in the different age groups is summarized and dosages are given. Artificial feeding, fluid and electrolyte management, antibiotics, and shock are also reported upon in a summarizing form.

The author mentions in this short book more than 45 times a "do not," where general surgical considerations alone and common sense in lack of special knowledge might lead to an action which has proved to be contraindicated in childhood. On the other hand, there are at least 40 clear cut "musts," implicating almost absolute indications.

The book appears to be an aid of considerable practical value for the general surgeon who deals with pediatric surgery, as well as for the resident in surgical training. It may also be considered a valuable guide for the general practitioner in coping with emergencies in children, infants, and newborns.

—*Johannes L. Leonhardt.*

THE VOLUME of *Pediatric Neurosurgery*[7] edited by Jackson and Thompson brings realization to the fact that neurologic surgery in the infant and child is becoming a prominent subspecialty of neurosurgery, isolated to a degree from that of adult neurosurgery. Similar to most modern books on surgery or other major subjects, this volume consists of a series of monographs written by 24 authors. All phases of pediatric neurologic surgery are included. The introductory chapters by the editors are well written and emphasize that pediatric neurosurgery is a distinct specialty. The chapter on preoperative and postoperative care merits careful study. Many points are brought out which one who works mainly with adults might neglect in treating children. Congenital malforma-

[6] DRINGLICHE CHIRURGIE BEIM SAUGLING UND KIND. By Doz. Dr. Dr. H.-E. Grewe. 189 pages, 60 illustrations. $5.95. Stuttgart: Georg Thieme Verglag, 1959.

[7] PEDIATRIC NEUROSURGERY. Edited by Ira J. Jackson, M.D., M.Sc., F.A.C.S., F.A.C.A., and Raymond K. Thompson, M.D., F.A.C.S. 564 pages, illustrated. $16.50. Springfield, Ill.: Charles C Thomas, 1959.

tions are briefly, but well, covered. Surgery of hydrocephalus is likewise descriptively written and includes an analysis of all accepted methods in the surgical treatment. Vascular malformations are discussed in detail, including diagnostic and therapeutic measures. The chapter on tumors, intracranial and cranial, constitutes a classic monograph, which alone makes the volume worthy of owning and studying. The reviewer thoroughly enjoyed the book and believes that it is a welcome and worthy addition to neurosurgical literature. Perhaps, if criticism were to be made of the book, the only one would be that the individualistic styles of the various authors might be modified to conform to a more uniform style, if this could be done without losing the individual thinking and reasoning. —*David Cleveland.*

THERE ARE 212 PAGES in the little book entitled *Open Reduction of Common Fractures*[8] involving the upper and lower extremities. The first 38 pages are devoted to the principles of open reduction and this is an excellent section for the student as well as the postgraduate student, surgeon, and orthopedic surgeon. The principles are described in detail with attention given to the care of soft tissues and bone.

The book is divided into two sections—fractures of the upper extremity and fractures of the lower extremity. The indications for surgery are outlined. The surgical approach is presented and, in many instances, illustrated with line drawings, and the technique of the operation is given in detail in each case. There is a short section at the end of each procedure relating the pitfalls and precautions which accompany each open reduction.

The book is an excellent little manual and will be of particular value to the general surgeon as well as to those in the training programs in orthopedic and general surgery. —*William A. Larmon.*

THE FIFTH EDITION of the time-honored text of *Orthopaedic Surgery*[9] offers the reader the benefits of the author's long experience at the University of Edinburgh. The fifth edition contains 1,075 pages compared to the 1,016 pages of the previous edition.

This book is intended primarily for the medical student, intern, and resident. As in the past, however, the contents have been arranged on a pathologic rather than an anatomic basis. This arrangement makes it difficult for the young reader to use the text as a reference. The index often is not useful in locating material. For the advanced student in orthopedic surgery, the limited bibliography usually leaves something to be desired.

As in most texts, statements or inferences are made with which a reader may be dissatisfied. For example, in the section devoted to so-called osteoclastoma, giant cell tumor, the variants such as aneurysmal bone cysts still are not clearly separated, and roentgen therapy is advocated as the treatment of choice. There is now evidence that such treatment converts some benign giant cell tumors to malignant lesions; and, in my opinion, it is to be avoided. The text still tells of excising the sacralized transverse process of a transitional fifth lumbar vertebra and of using silver wire in arthrodesis of the elbow. Both the surgical procedure for the back and use of the metal advocated for the wire have become antiquated.

With most of Sir Walter's teachings, I am in complete agreement; and he presents them in an easy, readable style. He and his colleagues are to be congratulated upon the fifth edition of this text which is rapidly becoming a classic. There are very few English-speaking orthopedic surgeons under the age of 60 years who have not used one edition or another of this text to study for board or fellowship examinations. —*Paul R. Lipscomb.*

A BEAUTIFUL LITTLE VOLUME entitled *The Physiology and Treatment of Peptic Ulcer*[10] is a worthy tribute to Lester R. Dragstedt to whom it is dedicated on the occasion of his retirement. It is written by 12 of his former students or clinical associates including internists and a radiologist, as well as surgeons, and is edited by J. Garrott Allen. The first part of the book deals with basic gastric physiology and the abnormalities responsible for ulcer formation. The authors have blended skillfully the descriptions of classic experiments with the clinical correlations and lessons. Unusually clear line drawings effectively supplement the written text and increase the pleasure of the reader. Another pleasing aspect of the volume is that the various contributors have obviously read each other's chapters and, thus, not only have avoided needless repetition but also have created a type of continuity not ordinarily found in volumes with multiple authorship.

A splendid chapter on "X-ray Diagnosis and Treatment of Peptic Ulcer" gives full details of the apparatus used and techniques employed, including a full page on how to prepare a palatable barium mixture. This reviewer knows several radiologists who should learn the formula! Various types of ulceration are excellently shown in numerous illustrations. A brief resumé of results after x-ray treatment of patients with gastric or duodenal ulcer omits details of the methods by which patients were selected and does not comment on the propriety of fairly heavy abdominal irradiation, 1,650 roentgens, for a benign ulcer. In a later chapter, one paragraph is devoted to irradiation of the stomach and it is stated that harmful effects have not been observed.

Surgeons will be particularly interested in chapters dealing with the rationale of various operations, evaluation of results after vagotomy and gastroenterostomy for duodenal ulcer in a series of 724 patients from the University of Chicago, and the continuing controversy over medical versus surgical treatment of the small gastric ulcer. In the preface it is stated that "No attempt has been made to

[8] OPEN REDUCTION OF COMMON FRACTURES. By Oscar P. Hampton, Jr., M.D., F.A.C.S., and William T. Fitts, Jr., M.D., F.A.C.S. 212 pages, 72 illustrations. $8.75. New York and London: Grune & Stratton, 1959.

[9] ORTHOPAEDIC SURGERY. By Sir Walter Mercer, M.B., Ch.B. (Edin.), M.Ch.Orth.(Liv.) (Hon.), F.R.C.S.(Hon.), F.R.C.S. (Eng.) (Hon.), F.C.S.So.Af.(Hon.), F.R.S.(Edin.). 5th ed. 1075 pages, 422 illustrations. $12.00. Baltimore: The Williams & Wilkins Co., 1959.

[10] THE PHYSIOLOGY AND TREATMENT OF PEPTIC ULCER. By J. Garrott Allen, Editor and collaborators. 236 pages, illustrated. $7.50. Chicago: The University of Chicago Press, 1959.

reconcile differing points of view. . . ." and instead ". . . the authors have been encouraged to present their own viewpoints." Most surgeons will favor the view of the author who advises that "The vast majority of proved chronic gastric ulcers should receive prompt surgical therapy." Conversely, most surgeons will politely disagree with the author who states: "Nevertheless, using the available modern diagnostic procedures, the accuracy of differentiation between benign and malignant gastric ulcer should be greater than 98 per cent"; and will regard accuracy of this order a hope for the future rather than an accomplishment of the present!

Other noteworthy features of the book are the development of the concept that ". . . gastric ulcer is caused by excessive gastric secretion due to antrum hyperfunction from stasis of food"; a quotation from Dr. Dragstedt on "What Would I Do If I Had an Ulcer?" which should be required reading for all surgeons who operate upon the stomach, irrespective of their current views; and useful bibliographies at the end of many of the chapters. The thoroughness with which the literature has been searched is perhaps best exemplified by reference No. 64 in Chapter 2, in which Paige, L. (Satchel), cited by J. J. Hobson, *Memphis Medical Journal*, 1957, 32: 273, is quoted for his rules on how to stay young, and which, the book states, are equally applicable to those who wish to avoid the development of an ulcer: "(1) Avoid fried meats which angry up the blood. (2) If your stomach disputes you, lie down and pacify it with cool thoughts. (3) Keep the juices flowing by jangling around gently as you move. (4) Go very light on the vices, such as carrying on in society. The social ramble ain't restful. (5) Avoid running at all times. (6) Don't look back. Something might be gaining on you."

—*Stanley O. Hoerr.*

ONE OF THE PHENOMENA of the midtwentieth century is the international symposium, the organizers of which have access to financial resources outstripping those of the average university or professional society. The protocol of such gatherings varies only in minor details, such as the nature of the transcript of the proceedings. The present volume of *Roentgens, Rads, and Riddles*[11] is an edited version of the stenotype record of a conversation, in 1956, among 75 roentgenologists and scientists interested in supervoltage radiation therapy. According to the Editors, "Speakers were specifically advised that we were not interested in new research or in gathering facts but rather in bringing together the opinion of a diverse body of experience." In spite of this admonition, the text contains a considerable amount of factual material and some interesting reports on research in radiation therapy. The approximately verbatim nature of the record makes it difficult for the reader readily to distinguish between opinion and fact, with the result that one closes the book with a feeling of confusion. Unfortunately, the Editors chose not to provide an index, thus, increasing the reader's difficulties. This reviewer devoted a considerable effort to *Roentgens, Rads and Riddles* in the preparation of these comments, but found himself unable to present a satisfactory summary of the symposium. The experts agreed that supervoltage radiation therapy was less damaging to the skin than conventional 250 kilovolts peak x-rays. A greater depth dose can be achieved; and, given suitable devices for directing the beam of radiation, injury to healthy tissue can be reduced. A great deal of ingenuity, effort, and money has been devoted to the construction and operation of supervoltage apparatus; but there has not been the improvement in the rate of cure of cancer which was anticipated by its early proponents.

Since the book contains a variety of opinions on each of these points, the reader is free to draw his own conclusions about the present status and the future importance of multimillion volt x-ray machines and of large cobalt 60 sources. It is difficult to judge the significance of the transcript of a symposium of this sort. It is the kind of thing that is read once and discarded, like a newspaper or a popular periodical. In spite of the eminence of many of the participants, the volume is neither a textbook, nor a reference work, nor a monograph. One suspects that the gentlemen who attended the symposium got a great deal more out of it than will the average reader of the record.

—*George V. LeRoy.*

THE FOURTH EDITION of the textbook *Experimental Surgery*[12] has maintained the excellency of the previous editions and has been enhanced by the addition of the pertinent advances made in the areas included in its subject material. The more important new material that has been added deals with the prostate gland, hypothermia, experimental surgery of the central nervous system, vascular surgery, and transplantation of tissue. There are also minor alterations dispersed throughout the book, indicating that the authors are keeping the material up to date. The value of the addition of the two veterinary authors is again attested to in this edition. The print and illustrations are excellent. The recommendations for this textbook are succinctly summed up in the closing sentence of the foreword by T. Lloyd Jones, "*Experimental Surgery* will be treasured alike by the busy specialist needing a reference book of information—established and new—and by those fortunate enough to be engaged in endeavors involving collaboration between workers in human medicine and veterinary medicine."

The foreword also contains the sentence: "Experimental surgery is physiology, as created by the tools of the surgeon." This reviewer emphatically does not agree with this statement. Experimental surgery is much more important than just another tool for physiology, even though it has been of extraordinary value in this regard. It is a discipline in its own right. Primarily, it is the art of surgery. It embraces many

[11] ROENTGENS, RADS, AND RIDDLES. A Symposium on Supervoltage Radiation Therapy, held at the Medical Division, Oak Ridge Institute of Nuclear Studies, July 15, 16, 17, and 18, 1956. Edited by Milton Friedman, M.D., Marshall Brucer, M.D., and Elizabeth Anderson, U. S. Atomic Energy Commission. 495 pages, illustrated. $3.50 (paper bound). Washington: U. S. Government Printing Office, 1959.

[12] EXPERIMENTAL SURGERY; INCLUDING SURGICAL PHYSIOLOGY. By J. Markowitz, M.B.E., M.B.(Tor.), Ph.D., M.S. in Exp. Surg.(Minn.), J. Archibald, D.V.M., M.V.Sc., Dr. Med. Vet (Giessen), M.R.C.V.S., and H. G. Downie, D.V.M., M.S. (Cornell), M.V.Sc. 4th ed. 931 pages, 580 illustrations. $12.50. Baltimore: The Williams & Wilkins Co., 1959.

objectives pertaining only to it, such as: (1) to afford opportunity to the surgeon and veterinarian for acquiring surgical technique, (2) to develop new surgical procedures, (3) to serve as a surgical tool in physiologic and pathologic research. The reason for the exploitation of experimental surgery as physiology resides in the fact that its employment has been so productive as a tool in physiologic research. It should be emphasized in this regard that operation comes first and the accuracy of the physiologic data and the conclusions based upon them depends upon the accuracy of the surgical technique employed. There would probably be a measurably fewer number of research publications if this fact had been recognized and adhered to. Above all, a laboratory of experimental surgery as depicted by Markowitz and associates in an inimitable manner should be a teaching laboratory dealing with activities and objectives which do not pertain to any other laboratory.

—*F. C. Mann.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Essentials of Orthopaedics. By Philip Wiles, M.S. (Lond.), F.R.C.S. (Eng.), F.A.C.S. 3rd ed. 576 pages, 417 illustrations. $13.00. Boston: Little, Brown & Co., 1959.

Textbook of Otolaryngology. By David D. DeWeese, M.D., and William H. Saunders, M.D. 464 pages, 354 illustrations. $8.75. St. Louis: The C. V. Mosby Co., 1960.

Interpersonal Relationships in the Hospital. By Warner F. Bowers, M.D. 125 pages, $5.00. Springfield, Ill.: Charles C Thomas, 1960.

New and Nonofficial Drugs; an Annual Compilation of Available Information on Drugs, Including Their Therapeutic, Prophylactic and Diagnostic Status, as Evaluated by the Council on Drugs of the American Medical Association, 1960. 768 pages, $3.35. Philadelphia and Montreal: J. B. Lippincott Co., 1960.

Clinical Obstetrics and Gynecology. A Quarterly Publication. Vol. II, No. 4, December 1959. Cesarean Section. Edited by Edwin J. De Costa, M.D. Advances in Gynecologic Surgery. Edited by S. B. Gusberg, M.D. 300 pages, $18/year. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, 1959.

Le traitement par la vitamine a de l'avortement a répétition (maladie pro-abortive endocrinienne récidivante des Smith). By O. Roujansky. 84 pages. 7,50 NF. Paris: L'Expansion Scientifique Française, 1960.

L'Apparato joideo; anatomia, fisiopatologia e clinica (ricerche ed osservazioni personali). Collana di Monografie. N. 3. By Lorenzo Marcucci. 165 pages, illustrated. Parma, Italy: L'Ateneo Parmense, 1959.

Klinische Chirurgie fuer die Praxis. Edited by Prof. Dr. med. O. Diebold, Prof. Dr. med H. Junghanns, and Prof. Dr. med. L. Zukschwerdt. Vol. I, No. 2. 144 pages, 43 illustrations. $6.40. Stuttgart: Georg Thieme, 1960.

Functional Anatomy of the Limbs and Back; a Text for Students of Physical Therapy and Others Interested in the Locomotor Apparatus. By W. Henry Hollinshead, Ph.D. 2nd ed. 403 pages, 159 illustrations. $9.00. Philadelphia and London: W. B. Saunders Co., 1960.

The Older Patient. By 21 authors. Edited by Wingate M. Johnson, M.D. 589 pages, illustrated. $14.50. New York: Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, 1960.

Treatment of Urinary Lithiasis. Edited by Arthur J. Butt, M.D., F.A.C.S. 577 pages, illustrated. $21.00. Springfield, Ill.: Charles C Thomas, 1960.

Back Pain; Diagnosis and Treatment Using Manipulative Techniques. By John McM. Mennell, M.D. 226 pages, 78 illustrations. Boston and Toronto: Little, Brown & Co., 1960.

Primary Tumors of the Calvaria; with Special Consideration of the Clinical Problems. By Franklin Jelsma, M.D. 116 pages, illustrated. $7.00. Springfield, Ill.: Charles C Thomas, 1960.

Cardiac Resuscitation. Edited by J. Willis Hurst, M.D. 141 pages, illustrated. $5.50. Springfield, Ill.: Charles C Thomas, 1960.

Zabriskie's Obstetrics for Nurses. By Elise Fitzpatrick, R.N., M.A., and Nicholson J. Eastman, M.D. 10th ed. 571 pages, illustrated. $6.00. Philadelphia and Montreal: J. B. Lippincott Co., 1960.

Atlas of Anatomy and Surgical Approaches in Orthopaedic Surgery; Upper Extremity. By Rodolfo Cosentino, M.D. With a Preface by Arthur Steindler. 192 pages, 134 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1960.

Current Therapy—1960; Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D. 808 pages. $12.00. Philadelphia and London: W. B. Saunders Co., 1960.

Christopher's Textbook of Surgery. Edited by Loyal Davis, M.D. 7th ed. 1,551 pages, 1,597 illustrations. $17.00. Philadelphia and London: W. B. Saunders Co., 1960.

Recent Advances in Surgery. Edited by Selwyn Taylor, D.M., F.R.C.S. Foreword by Sir James Paterson Ross, K.C.V.O., M.S. 5th ed. 500 pages, 160 illustrations. $13.00. Boston: Little, Brown & Co., 1959.

Oxygen Supply to the Human Fetus. A Symposium organized jointly by The Council for International Organizations of Medical Sciences. Established under the joint auspices of UNESCO and WHO and the Josiah Macy Jr. Foundation. Edited by James Walker and Alec C. Turnbull. Assisted by Clement A. Smith and Donald H. Baron. 313 pages, illustrated. $10.50. Springfield, Ill.: Charles C Thomas, 1960.

Diabetes; with a Chapter on Hypoglycemia. By 54 authors. Edited by Robert H. Williams, M.D. 793 pages, 192 illustrations, 23 in color. $20.00 New York: Paul B. Hoeber, Inc., Medical Division of Harper & Bros., 1960.

X-Ray Technology. By Charles A. Jacobi, B.Sc., R.T., M.T., and Donald E. Hagen, R.T. 2nd ed. 453 pages, 320 illustrations. $10.00. St. Louis: The C. V. Mosby Co., 1960.

Carter's Microbiology and Pathology. By Alice Lorraine Smith, M.D. 7th ed. 742 pages, 316 illustrations. $7.50. St. Louis: The C. V. Mosby Co., 1960.

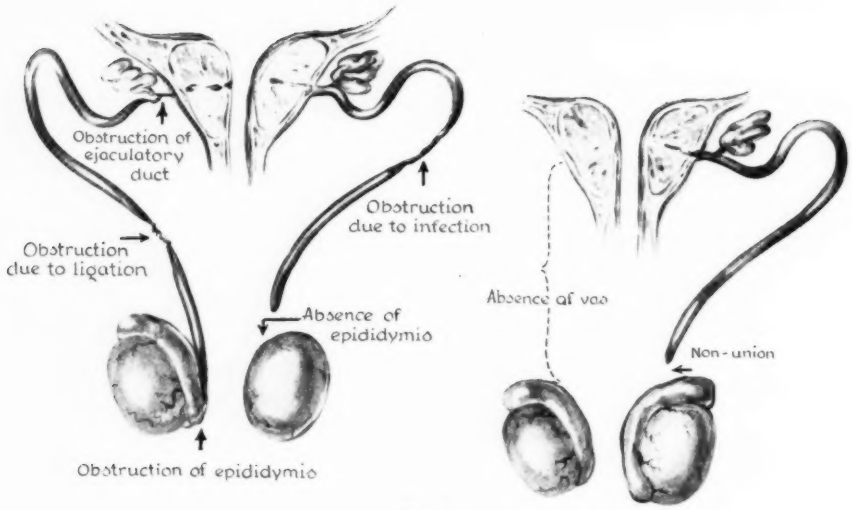

FIG. 1.

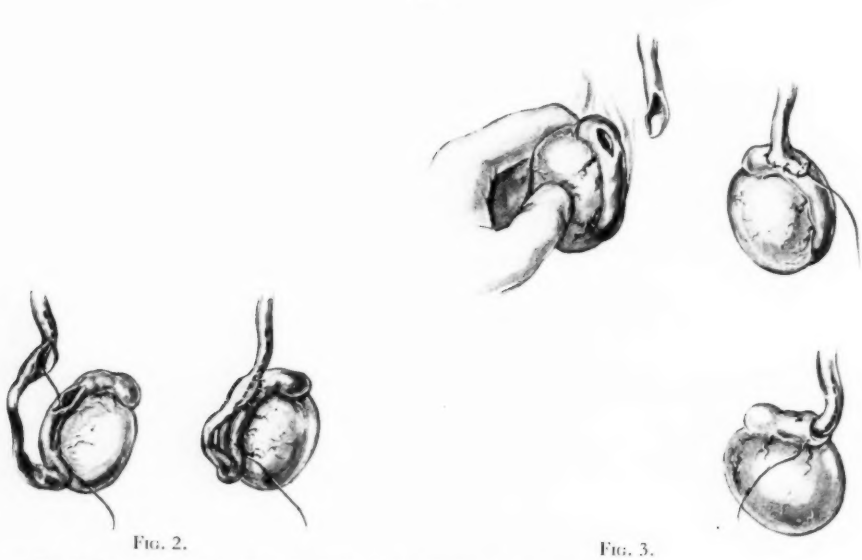

FIG. 2.

FIG. 3.

FIG. 1. Anatomic causes of azoospermia in the presence of normal testes.
FIG. 2. Epididymovas anastomosis indicated in obstruction of the globus minor.
FIG. 3. Termino-terminal epididymovas anastomosis with splint.